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Drinking Water Criteria Document for Cyanide (Final Draft)

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DRINKING WATER CRITERIA DOCUMENT FOR CYANIDE

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OFFICE OF DRINKING WATER

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The Office of Drinking Water (ODW), U.S. Environmental Protection Agency has prepared a Drinking Water Criteria Document on cyanide. This Criteria Document is an extensive review of the following topics:

- Physical and chemical properties of cyanides
- Toxicokinetics and human exposure to cyanides
- Health Effects of cyanides in humans and animals
- Mechanisms of toxicity of cyanides
- Quantification of toxicological effects of cyanides

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I. SUMMARY

Hydrogen cyanide and the alkali-metal cyanides are very soluble in water and, except for HCN, are not very soluble in organic solvents. The alkaline earth metal cyanides, in general, are not very soluble in water. HCN is volatile, and in aqueous solution is a very weak acid. The alkali-metal salts of cyanides are easily hydrolyzed in an aqueous solution. The metal cyanides can be oxidized to isocyanate and ultimately to CO_2 and N_2 in the presence of strong oxidizing agents. Some of the complex metal cyanides, such as the ferrocyanides and ferricyanides liberate HCN when the solutions are exposed to sunlight.

The fate of cyanides in the aquatic media may vary widely. Hydrogen cyanide and the most common alkali-metal cyanides may be lost from aquatic media primarily through the volatilization process. Some of these cyanides may also be lost through microbial degradation in aquatic media and sorption through particulate matters in water. However, both these processes are less significant than volatilization.

The sparingly soluble metal cyanides, such as CuCN in acidic waters (pH <7) may form some HCN that may subsequently volatilize from water. But the predominant fate of these compounds is sedimentation and microbial degradation.

The fate of water soluble complex metal cyanides, such as ferrocyanide and ferricyanides, with respect to biodegradation is not known with certainty. In the absence of destabilizing factors in water (high temperature, sunlight, extreme pH conditions), these complexes are expected to have long lifetimes and can be transported in the aquatic media.

The simple metal cyanides and HCN do not bioaccumulate in aquatic organisms. The water soluble complex metal cyanides may bioaccumulate to some extent in aquatic organisms although the bioaccumulation factors for such compounds are not known.

Cyanides are readily absorbed from the lungs, the gastrointestinal tract and the skin. Inhalation exposure to HCN provides the most rapid route of entry, resulting in the most rapid onset of toxic affects. Cyanide enters erythrocytes and is found in the blood at low levels in normal humans. Transplacental transfer can occur. Cyanide is detoxified by an intramitochondrial enzyme, rhodanese, which catalyzes the transfer of sulfur from a donor to cyanide to form the less toxic thiocyanate. Thiocyanate is excreted in the urine. Rhodanese is widely distributed throughout the body; high levels are found in the liver. Minor detoxification pathways include spontaneous reaction with cystine to form 2-imino-4-thiazolidinecarboxylic acid, and the reaction with hydroxycobalamin (vitamin B_{12}) to form cyanocobalamin. Both products are excreted in urine. The major route of cyanide elimination is via thiocyanate in the urine, although some cyanide enters the metabolism of 1-carbon compounds, and CO_2 is eliminated in expired air. A small amount of unchanged HCN is eliminated in expired air.

Signs of acute poisoning by cyanide include rapid breathing, gasping, tremors, convulsions and death. The severity and rapidity of onset of effects depend on route, dose, duration of exposure and compound administered. Inhalation exposure results in the most rapid absorption and appearance of toxic signs. Oral exposure to cyanide salts results in slower gastrointestinal absorption, passage to the liver and faster detoxification. The acute oral LD_{50} for cyanide is 4 mg CN^-/kg bw in rats and 3.4 mg CN^-/kg in mice. The LC_{50} for inhaled HCN by mice is 184 mg/m³. Species differ with respect to sensitivity with the dog being the most sensitive. Cyanide is less toxic when administered subchronically and chronically in the diet. Subchronic oral exposure to cyanide in capsules has resulted in histopathologic lesions in the central nervous system (CNS) of dogs. Subchronic and chronic subcutaneous administration of cyanide to rats also results in histopathologic damage to the brain and spinal cord. The results of chronic oral administration reveal no evidence of carcinogenicity. Negative results for KCN in the reverse mutation assay were obtained in five strains of *Salmonella typhimurium* with or without metabolic activation. A marginally positive response was found for HCN gas in strain TA100 of *S. typhimurium*. Cyanide was negative in a modified rec assay in *Bacillus subtilis*. Severe teratogenic effects of NaCN administered in high doses by subcutaneously implanted osmotic minipumps in hamsters were found.

Ingestion of cyanide by humans is fatal at doses of 0.5-3.5 mg/kg bw. Death, which is preceded by hyperventilation, vomiting, unconsciousness, convulsions, rapid heart rate, gasping and vascular collapse, occurs within 20 minutes of ingestion. A no-effect level for ingestion by humans is 0.06 mg CN^-/kg bw. The estimated 1-minute LC_{50} for inhalation of HCN by humans is 3763 mg/m³. Inhalations of ~2000 mg/m³ result in dyspnea, followed by rapid breathing, then apnea, gasping and death within minutes.

Many people are unable to smell cyanide, which has the odor of bitter almond, due to a sex-linked recessive gene. Sublethal concentrations produce dizziness, headache, confusion, nausea and numbness. Chronic oral exposure to HCN, KCN or NaCN in humans has not been described. Ingestion of cyanogenic plants, in combination with dietary deficiencies in protein, vitamin B_{12} and riboflavin, may result in neuropathies. Ingestion of cyanogenic chemicals combined with iodine deficiency may be associated with the etiology of goiter and cretinism. Other disorders associated with defective cyanide metabolism include tobacco amblyopia, retrobulbar neuritis and Leber's hereditary optic atrophy. Smoking during pregnancy may result in birth of low-weight infants. This may be partly due to the cyanide content of tobacco smoke. Case studies and epidemiological studies of workers occupationally exposed workers to cyanide describe effects such as headache, dizziness, nausea and thyroid enlargement.

Cyanide exerts its toxic effects by reacting with ferric iron (Fe^{+++}) in cytochrome oxidase, the enzyme that catalyzes the terminal step in the electron transport chain, thereby preventing utilization of oxygen by cells. The CNS and the heart are particularly sensitive to this histotoxic hypoxia. If the exposure to cyanide is high enough, the detoxification mechanism via rhodanese may be overloaded and toxic signs occur. Chronic or repeated exposure to high doses may result in repeated hypoxic insult to the CNS and degenerative changes in the CNS of rats and dogs.

Synergistic effects may occur if cyanide exposure is accompanied by exposure to other inhibitors of cytochrome oxidase, such as azide and sulfide. Treatments for cyanide poisoning are based on the generation or administration of compounds that can compete with cytochrome oxidase for cyanide. Sodium nitrite can generate methemoglobin which binds cyanide. Any compound that can act as a sulfur donor for rhodanese, such as sodium thiosulfate, can be an effective antidote. Cobalt-containing compounds can compete with cytochrome oxidase for cyanide and are also effective antidotes.

No suitable study was identified from which to calculate 1-day HAs. It is recommended that the 1-day HAs be set at the same level as the 10-day HAs. A 10-day HA for a 10 kg child is 0.22 mg/ℓ/day (0.22 mg/day or 0.02 mg/kg bw/day), and for a 70 kg adult is 0.75 mg/ℓ/day (1.50 mg/day or 0.03 mg/kg bw/day). A lifetime AADI for a 70 kg human is 0.75 mg/ℓ/day (1.5 mg/day or 0.02 mg/kg bw/day). Estimation of the concentration of cyanide in drinking water corresponding to increased lifetime risks of cancer of 10^{-4}, 10^{-5} and 10^{-6} is precluded by the lack of information on the carcinogenic effects of cyanides.

II. GENERAL INFORMATION AND PROPERTIES

Structure and Identification

Cyanides are a group of organic and inorganic compounds that contain the CN group. A large number of inorganic cyanides are used industrially, both as simple salts or as complex cyanides. Organic cyanides are known as nitriles, and compounds such as acrylonitrile and adiponitrile are the main cyanides produced in the United States (Towill et al., 1978). In this section, only a few widely used industrial inorganic cyanides will be discussed. The structure, molecular formula, molecular weight, Chemical Abstract Services (CAS) Registry number and Registry of Toxic Effects of Chemical Substances (RTECS) number of selected cyanides are given in Table II-1.

Physical and Chemical Properties

Physico-chemical properties (Weast, 1980; Towill et al., 1978) of selected cyanides are given in Table II-2.

Hydrogen cyanide is miscible with ethanol but is only slightly soluble in ether (Towill et al., 1978). Liquid HCN is unstable and can polymerize violently in the absence of stabilizers. In aqueous solutions, UV light may induce polymerization of HCN. Among the many polymerized products of HCN are the trimer, tetramer and other high molecular weight polymers (Cotton and Wilkinson, 1980).

In aqueous solution, HCN is a very weak acid having a pK_a (dissociation constant) value of 9.21 at 25°C (Cotton and Wilkinson, 1980). The

TABLE II-1

Structure and Identification Symbols of Selected Cyanides*

Compound	Molecular Formula	Molecular Weight	CAS No.	RTECS No.
Hydrogen cyanide; hydrocyanic acid; prussic acid; formo nitrile	HCN	27.03	74-90-8	MW6825000
Sodium cyanide	NaCN	49.01	143-33-9	VZ7525000
Potassium cyanide	KCN	65.12	151-50-8	TS8750000
Copper (1) cyanide; cupricin; cuprous cyanide	CuCN	89.56	544-92-3	GL7150000
Potassium ferricyanide; Tripotassium hexacyanoferrate	$K_3Fe(CN)_6$	326.27	13746-66-2	LJ8225000

*Source: NIOSH, 1982

TABLE II-2

Physical and Chemical Properties of the Selected Cyanides[a]

Compound	Physical State and Description	Melting Point (°C)	Boiling Point (°C)	Density (g/cm^3)	Vapor Pressure (mm Hg)	Water Solubility (g/100 mℓ)	K_{ow}[b]	Conversion Factor (1 ppm equivalent of mg/m^3)
HCN	colorless gas or liquid with bitter almond odor	-13.24	25.70	0.688 at 20°C (liquid)	807.2 at 27.2°C	completely miscible	0.66[c]	1.123
NaCN	colorless crystalline solid	563.7	1496	1.60-1.62[d]	0.76 at 800°C	48 at 10°C	-0.44[e]	2.037
KCN	colorless crystalline solid	634.5	NA	1.553 at 20°C	NA	71.6 at 25°C	NA	2.707
CuCN	white crystalline solid	473 (in N_2)	decomposes	2.92[d]	NA	insoluble[f]	NA	3.722
$K_3Fe(CN)_6$	red crystalline solid	decomposes	NA	1.85 at 25°C	NA	33 at 4°C	NA	13.561

[a] Adapted from Weast (1980) and Towill et al. (1978) unless otherwise stated.

[b] K_{ow} is the octanol/water partition coefficient

[c] Calculated average of values given by Leo et al. (1971)

[d] The temperature at which this value was measured is not available.

[e] Calculated by the method of Leo et al. (1971) from the value given by Hansch and Leo (1979)

[f] The exact solubility data is not available.

NA - Not available

relationship of pH to percent undissociated HCN in aqueous solutions at 25°C is shown below (Callahan et al., 1979):

pH	% undissociated HCN
<7	>99
8	93.3
9	58
10	13

Therefore, at pH below 8, most of HCN in aqueous media is present in the undissociated form.

The alkali-metal cyanides, NaCN and KCN, are less soluble in ethanol and methanol than in water (Weast, 1980). Since these compounds are ionic, their solubility in less polar and nonpolar organic solvents may be even lower than in alcohols. Both NaCN and KCN are strongly hydrolyzed in aqueous media, producing basic solutions. In the presence of strong mineral acids, the salts will liberate HCN from aqueous solutions (Towill et al., 1978).

The metal cyanides can be oxidized to isocyanate and ultimately to CO_2 and N_2 in the presence of strong oxidizing agents such as Cl_2 gas, O_3 gas, catalytic O_2 and peroxides. In fact, such processes, in addition to electrolytic decomposition, ionizing radiation, heat, activated carbon adsorption, ion floatation and liquid-liquid extraction are suitable for the treatment of cyanide wastes (Watson, 1973).

Copper (I) cyanide has a solubility product of only 3.2×10^{-20} in aqueous solution at ambient temperature (NIOSH, 1976); it is soluble in HCl and also in KCN and NH_4OH, with the formation of complexes (Cotton and

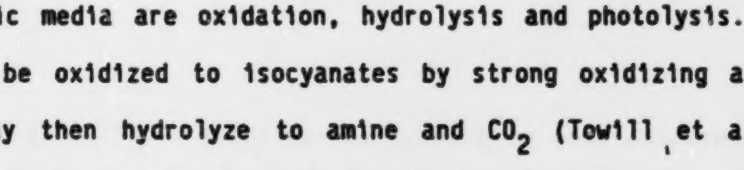
Wilkinson, 1980). In acidic solution, CuCN will form HCN which may be released from the aqueous phase. At a pH of 3, 78% of the cyanide may be removed from a 52 ppm CuCN solution in 30 minutes by the application of vacuum (Watson, 1973).

Potassium ferricyanide is less soluble in ethanol than in water (Towill et al., 1978). The aqueous solution is unstable and decomposes slowly on standing. This compound normally does not produce HCN or cyanide ions in water, but may produce HCN when exposed to sunlight or UV radiation (Towill et al., 1978).

Environmental Fate in Aquatic Media

The three likely chemical processes that may cause loss of simple cyanides in aquatic media are oxidation, hydrolysis and photolysis. Cyanides are known to be oxidized to isocyanates by strong oxidizing agents. The isocyanates may then hydrolyze to amine and CO_2 (Towill et al., 1978). Whether such oxidation and subsequent hydrolysis of isocyanates will significantly occur in natural waters known to contain peroxy radicals has not yet been determined.

The hydrolysis of alkali-metal cyanides proceeds rapidly in aquatic media, with production of HCN and alkali-metal hydroxides. The HCN produced may undergo further hydrolysis according to the following reaction (Callahan et al., 1979):



$$HCN \rightleftharpoons HCN: \xrightleftharpoons{H_2O} H\text{-}CO\text{-}NH_2 \xrightleftharpoons{H_2O} NH_4^+ + HCO^-$$

The reaction rate for the alkaline and acidic hydrolysis of HCN at the normal pH region (6-9) encountered in natural aquatic media is too slow (Callahan et al., 1979) to be significant in determining the fate of cyanides in aquatic media.

The photolysis of HCN and cyanide ions in aqueous solution was studied by Frank and Bard (1977). These compounds were found to be very resistant to photolysis with available sunlight. However, in the presence of TiO_2 powder, more than 99% of 26 mg/ℓ cyanide solution was oxidized in 2 days with sunlight irradiation (Frank and Bard, 1977), presumably through a heterogeneous photocatalytic oxidation process. However, such photocatalytic oxidation may not be very significant in natural aquatic systems because of significant light reduction at increasingly greater depths below the surface.

The photodecomposition of aqueous ferrocyanide and ferricyanide solution in sunlight, with the resultant production of HCN, has been observed (Callahan et al., 1979). A 5-hour sunlight exposure of 100 mg/ℓ potassium ferrocyanide produced cyanide ions at a concentration of 6 mg/ℓ (Callahan et al., 1979). While it is known that such compounds will photolytically produce HCN in sunlight, the importance of this photodecomposition process in determining the fate of ferrocyanide and ferricyanide in aquatic media cannot be determined unless the rate constants for these processes are known.

Several investigators have demonstrated that cyanides in aquatic media can be biodegraded at low concentrations by both single and mixed microorganisms (Callahan et al., 1979). Both aerobic and anaerobic microbial degradation of cyanide during sewage treatment plant operations have also been demonstrated (Callahan et al., 1979). It is evident from the literature that cyanides at low concentrations can be biodegraded in natural surface waters. However, additional data are needed to assess the relative importance of this process in determining the fate of aquatic cyanides. The studies by Raef et al. (1977a,b) indicate that volatilization of HCN from aquatic media may be a far more significant process for cyanides than biodegradation.

The two physical processes that contribute to the loss of cyanides from aquatic media are volatilization and sorption. In most natural waters, cyanides will be present both as CN^- and HCN. As has been shown in the Physical and Chemical Properties Section, the percent of HCN in aqueous solution increases with pH of the solution as shown on page II-4.

Since the pH of most natural waters ranges between 6 and 9, a large percent of cyanides will be present in the form of HCN. Hydrogen cyanide being extremely volatile (see Physical and Chemical Properties Section), the undissociated HCN is likely to volatilize from aquatic media. It has been shown that the half-life of HCN evaporation from solutions at concentrations of 25-200 μg/ℓ ranges from 22-110 hours in the laboratory. When the experiments were performed outdoors at moderate wind-speed, the rate of HCN loss increased by a factor of 2-2.5 (Callahan et al., 1979).

Hydrogen cyanide and alkali-metal cyanides are not likely to be strongly sorbed onto sediments because of high water solubilities. It was shown by Raef et al. (1977b) in an aerobic microbial biodegradation study of a cyanide, that the biological solids removed very little cyanide from solution through adsorption. From this result and the results of adsorption studies of other investigators (Callahan et al., 1979), it appears that sorption may not be an important reaction of water soluble cyanides in aquatic media.

There are no data available to indicate bioconcentration of cyanide in aquatic organisms. Using the equation of Veith et al. (1979) for the bioconcentration factor (BCF) of a chemical in whole fish (log BCF = 0.76 log K_{ow}) and the value of K_{ow} given in Table II-2, BCF values of 1.9 and 0.27 can be calculated for HCN and NaCN, respectively. According to U.S. EPA (1980), cyanides are not bioaccumulated in aquatic organism, and the concentration of cyanides in tissues is considered the same as the concentration of cyanide in the surrounding media. However, there is some evidence of bioaccumulation of metal cyanide complexes in fish, although the actual bioaccumulation factors are not known. It is difficult to assess the environmental significance of bioaccumulation of cyanide complexes since they are far less toxic than soluble HCN, NaCN and KCN.

Summary

Hydrogen cyanide and the alkali-metal cyanides are very soluble in water and except for HCN are not very soluble in organic solvents. The alkaline earth metal cyanides, in general, are not very soluble in water. Hydrogen cyanide is highly volatile, and in aqueous solution is a very weak acid.

The alkali-metal salts of cyanides are easily hydrolyzed in an aqueous solution. The metal cyanides can be oxidized to isocyanate and ultimately to CO_2 and N_2 in the presence of strong oxidizing agents. Some of the complex metal cyanides, such as the ferrocyanides and ferricyanides, liberate HCN when the solutions are exposed to sunlight.

The fate of cyanides in aquatic media may vary widely. Hydrogen cyanide and the most common alkali-metal cyanides may be lost from aquatic media primarily through volatilization. Some of these cyanides may also be lost through microbial degradation in aquatic media and sorption through particulate matters in water. However, both these processes are less significant than volatilization.

The sparingly soluble metal cyanides, such as CuCN, may form some HCN in acidic waters (pH <7) that may subsequently volatilize. However, the predominant fate of these compounds is sedimentation and microbial degradation.

The water-soluble complex metal cyanides, such as ferrocyanide and ferricyanide, may undergo some photodecomposition. The fate of these compounds with respect to biodegradation is not known with certainty. In the absence of destabilizing factors in water (high temperature, sunlight, extreme pH conditions), these complexes are expected to have long lifetimes and they can be transported in the aquatic media.

The simple metal cyanides and HCN do not bioaccumulate in aquatic organisms. The water-soluble complex metal cyanides, on the other hand, may bioaccumulate to some extent in aquatic organisms although the bioaccumulation factors for such compounds are not known.

III. TOXICOKINETICS

Absorption

The cyanides are rapidly absorbed by animals and humans, whether exposure occurs by inhalation of HCN gas, by ingestion of the cyanide salts KCN or NaCN, or by dermal exposure to HCN gas or to aqueous solutions of HCN, KCN and NaCN.

Gettler and Baine (1938) reported some early observations of quantitative absorption data in dogs and humans. Three dogs received single gavage doses of KCN equivalent to 1.57, 4.42 and 8.40 mg HCN/kg bw (corresponding to amounts of 20, 50 and 100 mg HCN, respectively. The dogs died within 155, 21 and 8 minutes, respectively, after dosing. At necropsy, the amount of HCN remaining in the GI tract was measured. The difference between the amount administered and the amount remaining in the GI tract was considered to represent the amount absorbed. According to this definition, the low-dose dog absorbed 14.4 mg of the administered 20 mg or 1.13 mg/kg bw (72%). The dog that received 50 mg HCN absorbed 12 mg or 1.06 mg/kg bw (24%). The dog that received 100 mg HCN absorbed 16.6 mg or 1.39 mg/kg bw (16.6%). Recent evidence that thiocyanate, the primary metabolite of cyanide (see Metabolism Section), undergoes GI recirculation in rats maintained on diets containing KCN (Okoh and Pitt, 1982) is discussed in the Excretion Section. However, Gettler and Baine (1938) employed analytical methods valid at the time to determine and distinguish between cyanide and thiocyanate. Liebowitz and Schwartz (1948) reported a case of attempted suicide in which an 80 kg man had ingested an estimated 3-5 g (37.5-62.5 mg/kg bw) KCN and recovered. He vomited 0.5 hour following ingestion, and gastric lavage was performed immediately on admission to a hospital. Two hours after ingestion the concentration of HCN in blood was 200 mg/ℓ, giving an estimated total of 1200 mg HCN in blood (assuming a volume of 6 ℓ of blood) and 2400 mg HCN in the whole body. These HCN concentrations correspond to 192 mg CN^-/ℓ blood, and an estimated total of 1152 mg CN^- in blood and 2304 mg CN^- in the whole body.

Absorption of HCN across the GI mucosa proceeds rapidly because it is a weak acid with a pK_a of 9.2. The acidic environment in the stomach favors the unionized form of HCN and, hence, facilitates the absorption. The physiological pH of body tissues also favors the undisso- ciated species (U.S. EPA, 1980).

Quantitative data on absorption of HCN by inhalation in dogs was reported by Gettler and Baine (1938). The HCN gas was generated into an inhalation apparatus from a tube containing a solution of hydrocyanic acid. Exhaled cyanide was bubbled through a solution of sodium hydroxide. The amount of absorbed HCN was estimated by subtracting the amount of cyanide remaining in the apparatus from the initial amount in the tube. Although the original amount of HCN in the tube was not reported, one dog was calculated to have absorbed 16.0 mg (1.55 mg/kg bw) and the other dog 10.1 mg (1.11 mg/kg bw). These doses were fatal to the dogs in 15 and 10 minutes, respectively.

Absorption of low levels of cyanide by humans following inhalation can be inferred from data on blood levels of thiocyanate in cigarette smokers compared with nonsmokers (Wilson and Matthews, 1966). Although plasma levels of cyanide did not differ significantly between the two groups, smokers had significantly ($p<0.001$) higher levels of thiocyanate, presumably formed from metabolism of inhaled cyanide in cigarette smoke, than did nonsmokers.

The air concentrations of HCN resulting in certain blood levels in humans were tabulated by Knowles and Bain (1968). At >300 ppm (330 mg/m³), blood levels reached >10 mg/ℓ. Concentrations of >200 ppm (220 mg/m³), >110 ppm (111 mg/m³) and >50 ppm (55 mg/m³) in air resulted in blood levels of 8-10, 3-8 and 2-4 mg/ℓ, respectively. It was emphasized that wide variations exist, and the values were presented as examples. Humans retained ~60% of HCN in the lungs, following the inhalation of HCN (0.0005-0.02 mg/ℓ) through normal breathing by mouth (Landahl and Herrmann, 1950).

Cyanides can also be absorbed by the dermal route. Walton and Witherspoon (1926) held a test tube of 1-inch diameter containing liquid HCN against the shaved bellies of guinea pigs and observed signs of toxicity. Dogs that were exposed to HCN gas in a chamber that allowed their heads to be excluded from exposure also developed toxic signs.

Drinker (1932) reported that three men working in an atmosphere of 2% (v/v) (20,000 ppm or 22,000 mg/m³) HCN gas for 8-10 minutes developed symptoms of dizziness, weakness and throbbing pulse, despite the fact that they were wearing gas masks. Potter (1950) described a case of an HCN process worker who entered the chamber wearing a gas mask and protective clothing. While attempting to take a sample of hydrocyanic acid, he removed one glove, and some of the acid ran over his hand. Within 5 minutes, he became dizzy, had difficulty breathing and became unconscious.

Hydrogen cyanide, either liquid or gas, is more readily absorbed dermally than are the cyanide salts (Wolfsie and Shaffer, 1959), although cases of toxicity in humans have resulted from dermal exposure to solutions of KCN (NIOSH, 1976). Since HCN can be generated from solutions of KCN and NaCN, some absorption may be attributed to inhalation exposure (see Chapter II).

Distribution

Once cyanide is absorbed it is rapidly distributed by the blood throughout the body. Within the blood, a greater concentration of cyanide was found in erythrocytes than in plasma when HCN was administered (McMillan and Svoboda, 1982); however, this was not the case when KCN was administered (Farooqui and Ahmed, 1982). Farooqui and Ahmed (1982) studied the incorporation of radioactivity in the erythrocytes of rats treated orally with $K^{14}CN$ (5 mg/kg). Levels of radioactivity declined rapidly from whole blood and plasma with a small increase in erythrocytes over 24 hours. Following hemolysis, the majority of the radioactivity (94.32%) in the erythrocytes was found in the hemolysate rather than the membranes. The heme fraction contained 70% of the radioactivity while 14-25% and 5-10% were found in the globin and cell membrane, respectively. Since cyanide reacts readily with iron in the ferric state (Fe^{+++}) (Hartung, 1982; NIOSH, 1976), the accumulation of cyanide within erythrocytes is mainly due to the binding of the cyanide ion to Fe^{+++} in methemoglobin to form the nontoxic complex cyanomethemoglobin (Chen and Rose, 1952).

Feldstein and Klendshoj (1954) reported blood levels of cyanide in normal humans that ranged from 0-0.107 µg/mℓ with an average of 0.048 µg/mℓ.

Tissue levels of cyanide in humans fatally poisoned with cyanide have been obtained at autopsy. Ansell and Lewis (1970) tabulated the mean levels of cyanide found in postmortem samples of tissues (Table III-1). In examining the data, two issues should be noted. First, when the concentration found equals zero (as shown in the range column), a loss of HCN from the sample must be suspected. This could occur by volatilization between the time of death and the time of assay, or by metabolism of CN^- to SCN^- (which was not assayed). Secondly, the time between exposure and death depends on the dose of cyanide which in these cases, was unknown. If death occurred very rapidly, it is possible that the tissue distribution of cyanide was not complete and, therefore, tissue levels of cyanide could be irrelevant. Gettler and Baine (1938) found high cyanide levels in brains and livers of three humans who had ingested fatal doses of cyanide. The importance of analyzing many tissues to determine the route of exposure was emphasized by Finck (1969). Table III-2 presents the distribution of cyanide in tissues of three fatally poisoned humans. For case one, no lung tissue had been submitted to the toxicologist for analysis. Based on low levels of cyanide in the gastric contents, cyanide inhalation may be suspected. Cases two and three, however, demonstrated high levels in stomach contents following ingestion.

The differences in cyanide distribution following the oral and inhalation exposures in rats were examined by Yamamoto et al. (1982). Rats were treated by gavage with NaCN to give a dose of 7 and 21 mg CN/kg bw. Another group of rats inhaled HCN at concentrations that averaged 356 and 1180 ppm (392 and 1298 mg/m³, respectively). The results are presented in Table III-3. Since little difference in distribution was observed with respect to dose or concentrations, the authors combined the data. Although these

TABLE III-1

Mean Levels and Ranges of Cyanide Ion Concentration in Human Organs in Cases of Fatal Poisoning[a,b]

Tissue	No. of Cases with Quantitative Levels Available	Mean (mg %)	Range (mg %)
Blood	58	2.39	0-5.3
Brain	34	1.20	0-19.9
Liver	48	1.62	0-25.0
Kidney	34	0.61	0-2.8
Spleen	22	3.77	0-37.5
Stomach Contents	49	160.0	0.2-2800
Urine	17	0.08	0-0.96

[a] Source: Adapted from Ansell and Lewis, 1970

[b] Note: for variable routes of exposure

TABLE III-2

Cyanide Levels in Human Tissues and Fluids After Fatal Cyanide Poisoning[a]

Sample	Cyanide Content (mg/100 g or mg/100 mℓ)		
	Case 1[b]	Case 2[c]	Case 3[c]
Gastric contents	0.03	15	20
Lung	NA	0.90	0.70
Blood	0.50	0.75	0.80
Liver	0.03	0.40	0.50
Kidney	0.11	0.35	0.40
Muscle	NA	0.30	NA
Brain	0.07	0.25	0.06
Urine	0.20	0.20	NA
Fat	NA	0.20	NA

[a] Source: Adapted from Finck, 1969

[b] Death from inhalation of cyanide gas

[c] Death from ingestion of cyanide salt

NA = Not analyzed

TABLE III-3

Cyanide Concentrations in Various Organs of Rats Treated with NaCN Orally (A) or HCN by Inhalation (B)[a]

Organs[c]	(A) Dose[b]			(B) Concentration		
	7 mg/kg (n=10)	21 mg/kg (n=9)	Combined[d] (n=19)	392 mg/m^3 (n=12)	1298 mg/m^3 (n=12)	Combined[d] (n=24)
Blood	5.01 ± 1.61	4.79 ± 2.04	4.91 ± 1.78	2.91 ±0.41	3.11 ± 0.51	3.01 ± 0.46
Liver	7.53 ± 1.45 (161 ± 50)[e]	10.40 ± 2.17 (230 ± 47)	8.89 ± 2.30 (194 ± 59)	2.19 ± 0.77 (76 ± 29)	2.11 ± 1.10 (68 ± 32)	2.15 ± 0.93 (72 ± 30)
Lungs	5.44 ± 2.27 (114 ± 46)	6.30 ± 2.19 (146 ± 66)	5.85 ± 2.22 (129 ± 57)	4.78 ± 1.61 (170 ± 69)	4.08 ± 2.24 (141 ± 104)	4.42 ± 2.02 (156 ± 88)
Spleen	2.48 ± 0.98 (52 ± 22)	1.75 ± 0.50 (36 ± 12)	2.09 ± 0.88 (45 ± 19)	0.58 ± 0.28 (20 ± 9)	0.79 ± 0.81 (28 ± 24)	0.68 ± 0.60 (24 ± 18)
Brain	1.31 ± 0.47 (27 ± 8)	1.76 ± 0.70 (40 ± 8)	1.52 ± 0.43 (33 ± 10)	1.34 ± 0.54 (45 ± 14)	1.56 ± 0.38 (50 ± 10)	1.45 ± 0.47 (48 ± 12)
Time to death (minutes)	10.3 ± 4.3	3.3 ± 2.1	NA	9.6 ± 2.3	5.4 ± 0.9	NA

[a] Source: Yamamoto et al., 1982

[b] The dose is expressed as CN^-

[c] Organ levels are μg/g wet weight or μg/mℓ blood

[d] Combined means that the data from the two dose groups were combined

[e] The number in parentheses are the organ levels of CN expressed as mean % of the blood levels

NA = Not available

combined data are provided in Table III-3, one must examine the appropriateness of doing so. The results of time to death indicate that animals receiving 21 mg/kg bw died within significantly less time (average 3.3 minutes) than those receiving 7 mg/kg bw (average time to death 10.3 minutes). This suggests that a uniform body distribution of cyanide may not have been reached at the time of death of the animals receiving the higher dose. Therefore, the similarity of cyanide levels in organs from both groups may be due to differences in distribution. Thus, there is no justification for combining these data. Rats receiving higher doses or concentrations died sooner. In order to compare the distributions for the two routes of administration, the organ levels of cyanide were expressed as percentage of the respective blood levels. Higher levels relative to blood were found in liver and lungs following oral administration. The concentration in lungs exceeded that in blood following inhalation of HCN; no p values were provided by the investigators.

The pattern of distribution of cyanide may also depend on which compound is administered. Ballantyne et al. (1972) compared the tissue distribution of cyanide from KCN and HCN in rabbits following intramuscular injection. For either case, the administered dose of cyanide was 8 mg/kg. Levels of cyanide were measured in tissues of two groups of rabbits (6/group) at 0.5 hours after death. In another two groups of rabbits, the organs were perfused with saline in order to measure the actual tissue levels without interference from blood cyanide levels in the tissues. The results are presented in Table III-4. The higher levels of cyanide in blood and tissues following HCN rather than KCN administration were presumably due to the more rapid absorption and distribution of HCN. High levels of cyanide were found in perfused brain and liver.

TABLE III-4

Comparison of Cyanide Concentrations in Tissues from Rabbits Killed by HCN with Concentrations in Tissues from Rabbits Killed with KCN[a,b]

Tissue	Cyanide concentration mean ± standard error[c]		p^d
	HCN	KCN	
	Containing blood		
Skeletal muscle	35.0 ± 5.2	29.6 ± 2.4	<0.5
Kidney	74.7 ± 10.3	52.0 ± 11.0	<0.1
Liver	148.7 ± 32.3	82.0 ± 8.0	<0.1
Spinal cord	48.5 ± 4.9	36.8 ± 3.5	<0.1
Brain	145.3 ± 37.2	106.5 ± 12.4	<0.1
Whole blood	685.0 ± 83.0	453.0 ± 34.0	<0.05
Serum	275.0 ± 18.0	161.0 ± 21.0	<0.005
	Perfused with saline		
Skeletal muscle	9.3 ± 2.7	7.8 ± 2.4	<0.7
Kidney	11.0 ± 4.3	2.3 ± 1.1	<0.1
Liver	43.7 ± 13.5	6.5 ± 0.8	<0.025
Spinal cord	49.8 ± 14.7	22.5 ± 3.8	<0.2
Brain	289.0 ± 67.7	98.0 ± 5.0	<0.02
Whole blood	761.0 ± 129.0	438.0 ± 8.0	<0.05
Serum	261.0 ± 48.0	134.0 ± 8.0	<0.05

[a] Source: Ballantyne et al., 1972

[b] For both compounds the dose was equivalent to 8 mg CN^-/kg bw

[c] Concentrations expressed as μg CN/100 g tissue wet weight or μg CN/100 mℓ blood or serum

[d] Significance of difference in cyanide concentrations between animals killed with HCN and those killed with KCN

Cyanide does not accumulate in blood and tissues following chronic exposure. Howard and Hanzal (1955) treated rats with dietary concentrations of HCN of 100 and 300 ppm (mg/kg diet) for 2 years. At the end of the 2-year period, virtually no cyanide was found in plasma or kidneys. Low levels were found in erythrocytes (mean of 1.97 μg). Increased levels of thiocyanate, the less toxic primary metabolite of cyanide (see Metabolism Section) were found in plasma (1123 μg), erythrocytes (246 μg), liver (665 μg) and kidney (1188 μg).

Transplacental transfer of cyanide presumably occurs. Doherty et al. (1982) reported that administration of solutions of NaCN to pregnant hamsters by subcutaneous infusion using osmotic minipumps resulted in malformed fetuses (see Teratogenicity and Other Reproductive Effects Section in Chapter V); this finding, however, does not prove occurrence of transplacental transfer.

Metabolism

The major metabolite of cyanide is the less toxic thiocyanate (U.S. EPA, 1980; Williams, 1959; de Duve et al., 1955), formed by the transfer of sulfur from a sulfur donor to the cyanide ion by the enzymatic action of rhodanese (Lang, 1933). Rhodanese is the trivial name for thiosulfate: cyanide sulfurtransferase, EC 2.8.1.1. or 3-mercaptopyruvate:cyanide sulfurtransferase EC 2.8.1.2. (Pettigrew and Fell, 1973). The species and tissue distribution of rhodanese were investigated by Himwich and Saunders (1948); the results are presented in Table III-5. The activity of the enzyme was highly variable among species and tissues. In the dog, the highest activity of rhodanese was found in the adrenal gland, ~2.5 times greater than the

TABLE III-5

Rhodanese Activity in Tissues of the Dog, Rhesus Monkey, Rabbit and Rat (mg CN converted to CNS/g of tissue after 15 minutes)[a]

Tissue	Dog		Rhesus Monkey		Rabbit		Rat	
	Range[b]	Number of Observations	Range[b]	Number of Observations	Range	Number of Observations	Range	Number of Observations
Suprarenals								
whole	2.14-3.60 (5.46, 4.50)	6	0.14-1.35	3	1.24-3.94	2	0.27-0.41	2
cortex	2.86-5.62	2	ND	NA	ND	NA	ND	NA
medulla	0.27-1.12	2	ND	NA	ND	NA	ND	NA
Liver	0.78-1.46 (4.91, 6.28)	7	10.98-15.16 (5.98)	4	7.98-18.92	9	14.24-28.38	9
Brain								
cortex	0.34-0.92	7	0.27	1	1.41-1.44	2	0.70-0.72	2
caudate nucleus	0.27-1.06	7	0.34-0.50	2	0.13-0.18	2	ND	NA
midbrain	0.52-1.35	6	0.22-0.80	2	1.17-1.39	2	0.73-1.13	2
cerebellum	0.21-1.22	7	0.33	1	0.63-1.24	2	ND	NA
medulla	0.38-1.52	7	0.49-0.85	2	0.91	1	ND	NA
Spinal cord								
cervical	0.15-1.00	7	0.56-0.57	2	0.89-0.90	2	0.16-0.18	2
lumbar	0.12-0.84	4	0.20-0.52	2	0.35-1.74	2	0.23-0.27	2
sacral	0.16-1.41	4	0.23-0.28	2	0.59-1.10	3	0.56-0.74	2
Heart	0.11-0.14	6	0.48-0.82	3	ND	NA	ND	NA
Kidney	0.42-0.74	6	2.46-3.58	4	6.20-7.69	3	10.44-11.08	2
Testes	0.32-0.41	5	0.38-0.46	3	0.32-0.36	2	1.24-1.61	2
Epididymis	0.29	1	ND	NA	ND	NA	ND	NA
Ovaries	0.42	1	ND	NA	0.30	1	ND	NA
Lung	0.16-0.17	3	0.11-0.21	2	0.40	1	ND	NA
Spleen	0.10-0.14	2	0.12-0.34	2	0.20	1	ND	NA
Muscle	0.03-0.19	6	0.23-0.57	3	0.18	1	ND	NA
Intestine								
duodenum	0.05-0.11	3	ND	NA	ND	NA	ND	NA
jejunum	0.04	1	ND	NA	ND	NA	ND	NA

TABLE III-5 (cont.)

Tissue	Dog		Rhesus Monkey		Rabbit		Rat	
	Range[b]	Number of Observations	Range[b]	Number of Observations	Range	Number of Observations	Range	Number of Observations
Eye	0.02	1	ND	NA	ND	NA	ND	NA
Optic nerve	0.35	1	ND	NA	ND	NA	ND	NA
Salivary gland, parotid	0.05-0.36	3	0.99	1	ND	NA	ND	NA
Lymph node	0.08-0.13	2	ND	NA	ND	NA	ND	NA
Pancreas	0.14-0.28	4	0.12-0.44	2	ND	NA	ND	NA
Thyroid	0.05-0.94	3	ND	NA	ND	NA	ND	NA
Anterior pituitary	0.26	1	ND	NA	ND	NA	ND	NA
Whole blood	0.01-0.02	2	ND	NA	ND	NA	ND	NA
Erythrocytes	0.01-0.02	2	ND	NA	ND	NA	ND	NA
Plasma	0.01	1	ND	NA	ND	NA	ND	NA

[a] Source: Himwich and Saunders, 1948

[b] Figures in parentheses are single observations falling outside the normal range.

ND = Not determined; NA = Not applicable activity in liver. Monkeys, rabbits and rats had highest activity in liver and kidney, with relatively low levels of rhodanese in adrenals. It should be noted that the enzyme activity in the livers of monkeys, rabbits and rats was ~10-20 times higher than the activity in the liver of dogs, and that total activity in the other species was higher than that in dogs. Dogs are particularly sensitive to the acute effects of cyanide (see General Toxicity Section in Chapter V). Similar activities of the enzyme among the species were found for brain, testes, lungs, spleen and muscle. The ubiquitous nature of the enzyme was demonstrated in the dog for which low levels of rhodanese activity were also measured in erythrocytes, anterior pituitary, thyroid, pancreas, lymph nodes, salivary glands, optic nerve, eye, intestine and heart.

The activities of different compounds as sulfur-donors have been studied. Himwich and Saunders (1948) found that sodium thiosulfate (100% relative activity) was the best sulfur donor when compared with sodium sulfide (4%), thiourea (4.5%), α-naphthylthiourea (4.6%), thiouracil (1%) and cysteine (1%). No activity was measured when thiodiglycol, diphenyl sulfide or diphenyldisulfide were tested. Sorbo (1953) found that p-toluene thiosulfonate was approximately 4.5 times more active as a sulfur donor than thiosulfate, while ethyl thiosulfate, ethyl xanthate, diethyldithiocarbamate and hydrosulfite were relatively inactive. The structural requirements, therefore, were for a free sulfur to be adjacent to another sulfur atom in the molecule. Since the greatest activity of rhodanese is found in mitochondria (de Duve et al., 1955), and rhodanese is widely distributed among tissues (Himwich and Saunders, 1948), the rate limiting factor for cyanide detoxification to thiocyanate is the intracellular, and especially intramitochondrial, availability of an appropriate endogenous sulfur donor. The nature of the endogenous sulfur donor is unknown (U.S. EPA, 1980).

Pettigrew and Fell (1973) investigated cyanide-thiocyanate interconversion by administering KCN i.p. to Wistar rats fed either a normal diet or a vitamin B_{12}-deficient diet. Both groups received a daily dose of 9.2 µmole (0.6 mg) CN^-/100 g bw, 5 days/week for 3 weeks. This dose approximates the minimum dose which has previously been shown (Rose et al., 1954; Lessell, 1971) to produce neurological disturbances in rats. Among the vitamin B_{12}-deficient rats, the mean whole blood CN^- concentrations rose 6-fold while the mean plasma thiocyanate concentration rose 8-fold. Among the normally fed rats, blood was sampled at various intervals following the injection. The whole blood CN^- concentration rose quickly reaching a maximum ~20 minutes postinjection and then fell rapidly to minimal levels ~2 hours postinjection. Conversely, the plasma thiocyanate levels increased slowly, reaching a maximum between 1 and 4 hours postinjection after which it decreased gradually.

A detoxification rate of 0.076 mg/kg/minute was determined in guinea pigs during continuous intravenous infusion of cyanide (Lendle, 1964). The estimated detoxification rate in humans has been estimated as 0.017 mg/kg/minute (McNamara, 1976). This estimate was based on a study in men injected intravenously with HCN.

The overall rate of conversion of cyanide to thiocyanate will depend upon the rate of conversion of thiocyanate to cyanide. The rhodanese reaction was shown to be nonreversible; however, conversion of thiocyanate to cyanide was found to be mediated by a different enzyme, thiocyanate oxidase, which has been found in erythrocytes of humans, dogs, rabbits and rats (Goldstein and Rieders, 1951, 1952). A minor activity of the glutathione-S-transferases in converting organic thiocyanates to cyanide was reported by Habig et al. (1975).

The overall rate of detoxification of cyanide will also depend upon the contribution of minor pathways. Cyanide can react spontaneously with cysteine to yield 2-aminothiazoline-4-carboxylic acid which tautomerizes to 2-imino-4-thiazolidinecarboxylic acid (Wood and Cooley, 1956). Rats pretreated with ^{35}S-cystine excreted 16% of a subcutaneous dose of NaCN as ^{35}S-labeled 2-imino-4-thiazolidine-carboxylic acid in the urine. Thiocyanate in urine accounted for 80% of the cyanide dose.

Another minor route of cyanide detoxification is via the reaction of cyanide with the B_{12} vitamin, hydroxocobalamin, to yield cyanocobalamin, a complex which is an essential element, is nontoxic, and is excreted in urine (Brink et al., 1950; Boxer and Rickards, 1951) and bile (Herbert, 1975). A metabolic pathway involving the oxidation of cyanide to CO_2 and formate was studied by Boxer and Rickards (1952b). A dog injected with ~0.1 mg $^{14}CN^-$/kg, once an hour for 5 hours, excreted 0.007% of the dose as formate and 92% as thiocyanate over 2 days. Rats similarly treated with ^{14}CN (215 µg/rat/injection), excreted 1.7% of the dose in the expired air. Of this amount of radioactivity, 10% was $H^{14}CN$ and 90% was

$^{14}CO_2$. Thus, carbon derived from cyanate can enter one-carbon-compound metabolic pathways. The various pathways of cyanide biotransformation are summarized in Figure III-1.

Excretion

By far the major route of cyanide elimination from the body is via urinary excretion of thiocyanate. Rats eliminated 80% of subcutaneously-injected cyanide as thiocyanate in the urine, while 16% was eliminated as urinary 2-imino-4-thiazolidine-carboxylic acid (Wood and Cooley, 1956). A man who had ingested 3-5 g KCN (1.2 g HCN was estimated in blood, assuming 6 ℓ blood, 2 hours later) eliminated a total of 237.14 mg of thiocyanate in 72-hour urine (Liebowitz and Schwartz, 1948). Maliszewski and Bass (1955) found increased levels of thiocyanate in the urine, saliva and perspiration of cigarette smokers compared with nonsmokers. Okoh (1983) reported the pattern of elimination of ^{14}C in rats maintained on a diet of KCN (~2 mg CN^-/rat/day) for 6 weeks, and then injected subcutaneously with $Na^{14}CN$. Over 57% of the administered radioactivity was excreted in the 24-hour urine compared with 4.9% in expired air and 1.7% in feces. Thiocyanate accounted for 78.8% and cyanide for 1.3% of the urinary radioactivity. Of the radioactivity in expired air, 89.5% was $^{14}CO_2$ and 9.4% was $^{14}CN^-$. In a similar study, Okoh and Pitt (1982) also found radioactivity excreted in feces following intraperitoneal injection of $Na^{14}CN$. This finding, along with relatively high levels of radioactivity in the stomach wall and stomach contents compared with other tissues, suggested that GI recirculation was occurring. Approximately 80% of the radioactivity in the stomach contents was in the form of thiocyanate.

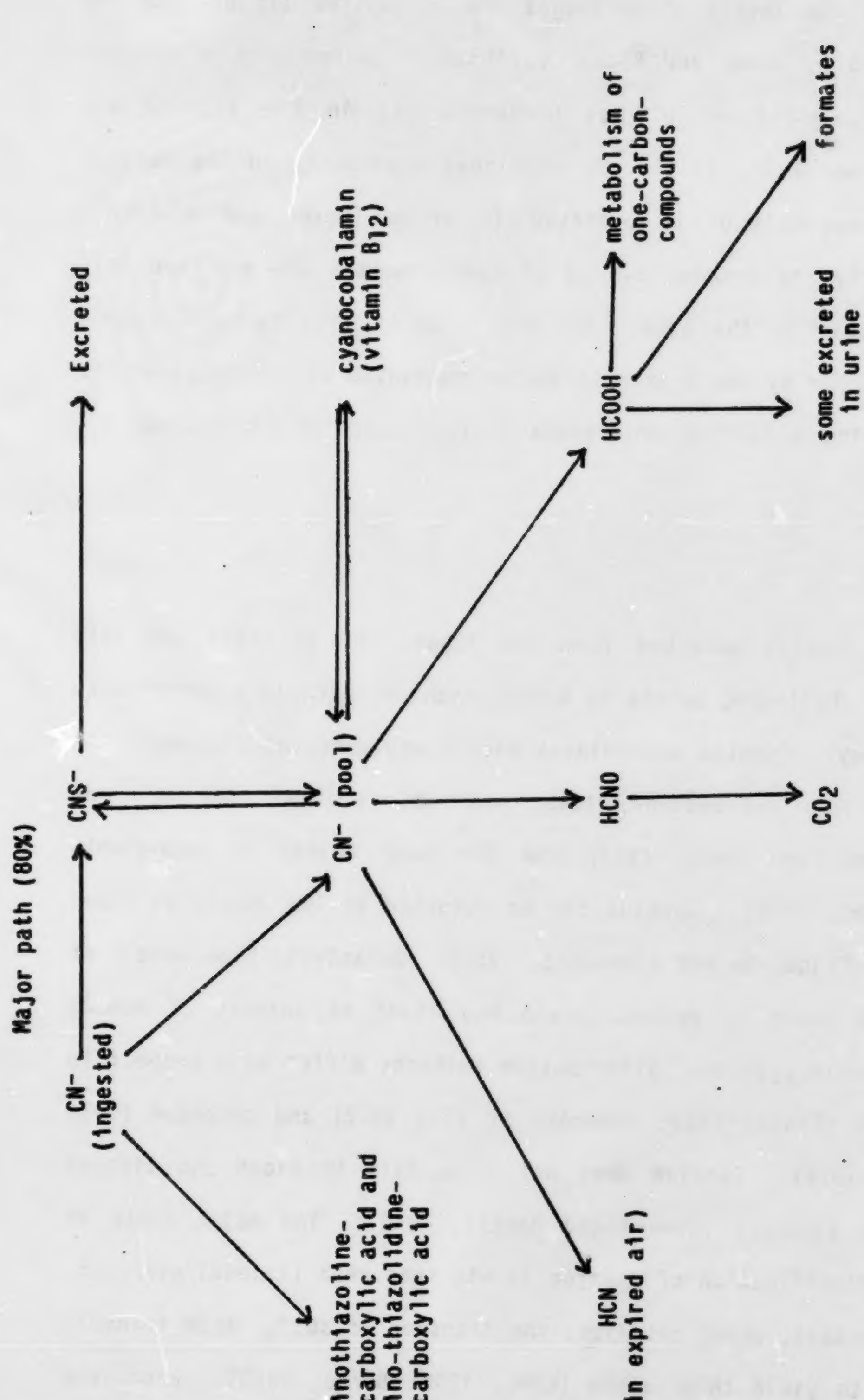

Major path (80%)
CN- (ingested)
CNS-
Excreted
CN- (pool)
cyanocobalamin (vitamin B_{12})
2-aminothiazoline-4-carboxylic acid and 2-imino-thiazolidine-4-carboxylic acid
HCN (in expired air)
HCNO
CO_2
HCOOH
metabolism of one-carbon-compounds
some excreted in urine
formates

FIGURE III-1

Fate of Cyanide in the Body

Source: Ansell and Lewis, 1970

The finding of low levels of unchanged HCN in expired air of rats and humans was reported by Boxer and Rickards (1952a). Guinea pigs eliminated 1-2% of intravenously-infused HCN as unchanged gas in the expired air (Friedberg and Schwarzkopf, 1969). As mentioned previously in the Metabolism Section, cyanocobalamin is excreted in urine (Boxer and Rickards, 1951). Additionally, in humans, 3-8 µg of cyanocobalmin are excreted into the GI tract, mainly in the bile. All but 1 µg of this excreted cyanocobalmin is reabsorbed by the intrinsic factor mechanism at the level of the ileum, thus allowing effective enterohepatic recirculation of vitamin B_{12} (Herbert, 1975).

Summary

Cyanides are readily absorbed from the lungs, the GI tract and skin (U.S. EPA, 1980). Following uptake by blood, cyanide is rapidly distributed throughout the body. Cyanide accumulates within erythrocytes (Farooqui and Ahmed, 1982; McMillan and Svoboda, 1982) where it combines with Fe^{+++} of methemoglobin (Chen and Rose, 1952) and the heme moiety of hemoglobin (Farooqui and Ahmed, 1982). Cyanide can be detected at low levels in blood of normal humans (Feldstein and Klendshoj, 1954). Relatively high levels of cyanide have been found in spleen, brain and liver at autopsy of humans fatally poisoned with cyanide. Distribution patterns differ with respect to route of exposure (Finck, 1969; Yamamoto et al., 1982) and compound (Ballantyne et al., 1972). Cyanide does not accumulate in blood and tissues following chronic exposure (Howard and Hanzal, 1955). The major route of metabolism and detoxification of cyanide is via rhodanese (thiosulfate:cyanide sulfurtransferase), which catalyzes the transfer of sulfur from thiosulfate to cyanide to yield thiocyanate (Lang, 1933; Sorbo, 1953). Rhodanese is widely distributed among organs of dogs, rabbits, rats and monkeys; high levels are found in the liver (Himwich and Saunders, 1948). The greatest activity of rhodanese is located in mitochondria (de Duve et al., 1955), and the enzyme is specific for a sulfur donor with a free sulfur atom adjacent to another sulfur atom in the molecule (Sorbo, 1953). Guinea pigs detoxified cyanide at a rate of 0.076 mg/kg/minute (Lendle, 1964). Minor detoxification pathways include the spontaneous reaction of cyanide with cysteine to form 2-imino-4-thiazolidinecarboxylic acid (Wood and Cooley, 1956), and the reaction of cyanide with hydroxocobalamin (vitamin B_{12a}) to yield cyanocobalamin (vitamin B_{12}) (Brink et al., 1950; Boxer and Rickards, 1951). Both of these compounds are excreted in urine. Cyanide can also be oxidized to CO_2 and formate (Boxer and Rickards, 1952b). The major route of cyanide elimination is via urinary excretion of thiocyanate (Wood and Cooley, 1956; Okoh, 1983). Small percentages of radioactivity derived from $Na^{14}CN$ administered intraperitoneally to rats were excreted in expired air and feces (Okoh, 1983). The fecal excretion, coupled with the detection of radioactivity in the stomach wall and contents following intraperitoneal injection of ^{14}CN, suggested GI recirculation (Okoh and Pitt, 1982).

IV. HUMAN EXPOSURE

Humans may be exposed to chemicals such as cyanide from a variety of sources, including drinking water, food, ambient air, occupational settings and consumer products. This analysis of human exposure to cyanide is limited to drinking water, food and ambient air because those media are considered to be sources common to all individuals. Even in limiting the analysis to these three sources, it must be recognized that individual exposure will vary widely based on many personal choices and on several factors over which there is little control. Where one lives, works and travels, what one eats, and physiologic characteristics related to age, sex and health status can all profoundly affect daily exposure and intake. Individuals living in the same neighborhood or even in the same household can experience vastly different exposure patterns.

In the Exposure Estimation Section of this chapter, available information is presented on the range of human exposure and intake for cyanide from drinking water, food and ambient air for the 70 kg adult male. It is not possible to provide an estimate of the number of individuals experiencing specific combined exposures from those three sources.

Exposure Estimation

Drinking Water. Essentially no information was obtained indicating the occurrence of cyanide in drinking water supplies. Only one of the Federal surveys [the 1969 Community Water Survey (CWSS)] included cyanide as an analyte.

The CWSS (McCabe et al., 1970) examined 120 surface water supplies, 613 groundwater supplies, 152 supplies with mixed water or purchased sources and 84 special systems (trailer parks, tourist and other institutions) in the United States in 1969. Samples were analyzed for various chemicals including cyanide. A total of 2595 distribution water samples were collected. The U.S. Public Health Service mandatory drinking water limit for cyanide in effect at the time of this study was 0.01 mg/ℓ. Cyanide concentrations in all samples were below this limit. The maximum cyanide concentration reported was 0.008 mg/ℓ.

According to U.S. EPA (1980), cyanide is an uncommon pollutant in U.S. water supplies. Levels in excess of the U.S. Public Health Service mandatory limit (McCabe et al., 1970) were not documented in U.S. EPA (1980). Apparently, the general recognition of the high toxicity of cyanide has made its removal standard practice in industry. As reported in U.S. EPA (1980), accidental perturbations have resulted in fish kills, livestock death and other environmental damage. Approximately 1500 drums (30 and 55 gallon) containing cyanides disposed near Byron, IL caused significant environmental damage and livestock death. Surface water runoff from the area was reported to contain up to 365 mg/ℓ of cyanide (Towill et al., 1978).

Given the lack of information on cyanide in public drinking water supplies, human intake of cyanide from drinking water could not be evaluated.

Diet. Although it is uncommon to find cyanide in foods in the United States, certain nitriles naturally occur in plants such as soybeans, lima beans and cassava (U.S. EPA, 1980; Honig et al., 1983). Honig et al. (1983)

found levels of cyanide <0.1 mg/kg in raw soybean meal and <1.5 mg/kg in soybean product samples tested under standard conditions. Honig and coworkers maintained that, according to the Food Protein Council (1978), consumption of edible soy protein products in the United States is >1 billion pounds annually, which is equivalent to <3 g of protein/person/day. The authors, therefore, concluded that soybean cyanide levels do not appear to be of nutritional significance.

Although the lima bean has been studied more than any other cyanogenetic plant food consumed by man (Leiner, 1966), none of these studies have focused on cyanide levels in lima beans consumed in the United States. Similarly, the cassava plant is used to produce tapioca, a food infrequently eaten in the United States; no studies have been conducted in the United States on cyanide levels in cassavas (Honig et al., 1983).

No data are available from the Food and Drug Administration (FDA) on the occurrence of cyanide in foods nor is any information available on the daily dietary intake of cyanide.

Air. No information is available on the levels of cyanide in ambient air.

Summary

Insufficient information was available to assess human exposure to cyanide or to determine the relative source contribution to total exposure by the three common media (drinking water, food and ambient air).

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V. HEALTH EFFECTS IN ANIMALS

General Toxicity

There are numerous studies on the toxic effects of the cyanides administered to animals by a variety of routes. In the current discussion, studies employing the oral route of administration are emphasized. No attempt was made to review all the studies employing other routes of exposure; however, several representative reports are included for the sake of integrity.

An important consideration in evaluating oral toxicity of cyanides is not only the total amount administered but also the rate of its absorption. This follows from the fact that the liver is the major site of cyanide detoxification; like any other enzymatically catalyzed reaction this detoxification reaches a maximum rate in the presence of excess substrate. If cyanide absorption proceeds too fast, the capacity of the liver to form thiocyanate upon first pass of mesenteric blood through the organ may be exceeded. In contrast, slow absorption of the same total oral load of the poison may permit the liver to completely metabolize it. Of course, cyanide is readily absorbed from the gastrointestinal tract, especially as at physiological pH it is present mostly in the highly diffusible nonionized form. However, the rate of this absorption may be influenced by factors such as the composition and volume of the intestinal contents and by the rate of peristalsis.

An additional problem with cyanide feeding studies is the likely loss of this substance by volatilization of HCN before the food is consumed. Even if attempts are made to chemically determine total cyanide loss, average concentrations of cyanide in food cannot be computed unless it is known whether such loss follows zero or first-order kinetics.

Two important conclusions follow from these considerations: use of feeding studies as the basis for the setting of water standards introduces a significant uncertainty in the case of cyanide, and this uncertainty must be recognized by introduction of a suitable uncertainty factor. Secondly, toxicity of injected cyanide may differ greatly from that of ingested cyanide because injection may cause the poison to reach the liver at a rate quite different from that following ingestion. Use of injection data for the purpose of setting permissible drinking water standards of cyanide therefore also suffers from additional uncertainty.

Acute Exposure. The lethal effects of cyanide exposure by any route are well known; however, the severity of effects and the time course depend upon the route, the dose, the duration and the compound administered. By far, inhalation of the HCN gas results in the most rapid absorption (see Absorption Section in Chapter III) and, hence, the most rapidly appearing signs. Gastrointestinal absorption of the salts, NaCN and KCN, is slower and results in passage through the portal system into the liver. Rhodanese, the enzyme(s) responsible for converting the cyanide ion into thiocyanate, is found in tissues throughout the body, but the major site in most species is the liver (see Metabolism Section in Chapter III). Therefore, first passage of cyanide into the liver followng gastrointestinal absorption results in a greater degree of detoxification than if cyanide is absorbed from the lungs. Cyanide exerts its toxic effect by reacting with the ferric ion (Fe^{+++}) in mitochondrial cytochrome oxidase, thereby interfering with cellular respiration (see Chapter VII). If enough cyanide can be detoxified before death supervenes, then recovery can occur (Di Palma, 1971).

Single-dose LD_{50} values for cyanides are presented in Table V-1. For the sake of comparison, all doses are represented as the dose of the administered compound, as well as the equivalent dose of cyanide ion. This practice is followed throughout this chapter in subsequent tabulations of dose-response data. Ballantyne et al. (1971, 1972) demonstrated that intramuscular administration of HCN to rabbits resulted in lower LD_{50}s than did intramuscular administration of KCN to rabbits with the LD_{50} for HCN in female rabbits being significantly lower; however, when expressed as dose of cyanide ion, the LD_{50}s were approximately equivalent. Oral LD_{50} values are available for NaCN and KCN. For NaCN, a human oral LD_{50} of 2.86 mg NaCN/kg bw (1.52 mg CN^-/kg bw) and a rat oral LD_{50} of 6.44 mg NaCN/kg bw (3.41 mg CN^-/kg bw) are reported (NIOSH, 1980). For KCN, oral LD_{50}s are reported as follows: 10 mg KCN/kg bw (4 mg CN^-/kg bw) for rats (Gaines, 1969; Hayes, 1967), 8.5 mg KCN/kg bw (3.4 mg CN^-/kg bw) for mice (Sheehy and Way, 1968), 5 mg KCN/kg bw (2 mg CN^-/kg bw) for rabbits (NIOSH, 1980) and 2.86 mg KCN/kg bw (1.14 mg CN^-/kg bw) for humans (NIOSH, 1980). Note that in the case of cyanide, such determinations differ from the classical determination of an LD_{50} (i.e., counting of deaths during 14 days after dose administration) since cyanide is extremely acutely toxic. In the LD_{50} determination in mice, the animals were observed for 24 hours because many mice that appeared to be dead recovered. Ferguson (1962) demonstrated the importance of the volume of the vehicle in determining toxic effects. A more dilute solution of KCN was more toxic to rats than a more concentrated one since the former was administrated in greater volume than the latter. The LD_{50} for intraperitoneal NaCN in mice (Kruszyna et al., 1982) is essentially the same as that for oral KCN in mice (Sheehy and Way, 1968), when expressed in terms of cyanide ion (3.2 vs. 3.4). KCN and NaCN have

TABLE V-1

Single-Dose LD_{50} Values for Cyanides

Route	Administered Compound	Species/Strain	Age/Weight (g)	Sex/No.	Vehicle	LD_{50} (mg/kg bw)	LD_{50} (mg CN^-/kg bw)	Comment	Reference
Oral	KCN	rat/Sherman	adult/NR	M/50	water	10 (8.7-11.5)	4 (3.5-4.6)	The rats died within 1 hour. The LD_1 was 5.9 mg KCN/kg bw (2.4 mg CN^-/kg).	Hayes, 1967; Gaines, 1969
Oral	KCN	mouse/Swiss-Webster	NR/NR	NR/20/group	water	10.8 (10.0-11.7)	4.3 (4.0-4.7)	The compound was administered in a volume corresponding to 5% bw.	Ferguson, 1962
						15.8 (14.6-17.1)	6.3 (5.8-6.8)	The volume corresponded to 1% bw.	
Oral	KCN	mouse/Swiss-Webster	NR/18-20	M/10/group	NR	8.5 (8.1-9.0)	3.4 (3.2-3.6)	The LD_{50} is for mice dying up to 24 hours after dose. Signs of toxicity appeared in 30-90 seconds. After a short period of convulsions, mice were moribund; many at doses below LD_{50} appeared dead but recovered.	Sheehy and Way, 1968
Ocular	HCN	rabbit/NR	NR/NR	NR/NR	see comment	1.05	1.01	It was stated that the toxicity of NaCN was not different whether applied in solution, as a solid or mixed with an inert powder. Deaths occurred in 3-12 minutes.	Ballantyne, 1983
	KCN					7.87	3.15		
	NaCN					5.05	2.68		
i.p.	NaCN	mouse/CD-1	NR/25-30	M/NR	water	6.0 (6.0-6.4)	3.2 (3.2-3.4)	Pretreatment of mice with hydroxylamine, dimethylaminophenol or sodium nitrite increased the LC_{50} of NaCN.	Kruszyna et al., 1982
s.c.	KCN	mouse/Swiss-Webster	NR/18-23	M/10/group	saline	8.5 (7.7-9.4)	3.4 (3.1-3.8)	LD_{50} increased by pretreatment with sodium nitrite and sodium thiosulfate.	Way et al., 1966a
s.c.	KCN	mouse/Swiss-Webster	NR/18-23	M/10/group	saline	12.0 (10.8-13.3)	4.8 (4.3-5.3)	LD_{50} increased by pretreatment with cobaltous chloride alone or in combination with sodium nitrite and/or sodium thiosulfate.	Isom and Way, 1973

TABLE V-1 (cont.)

Route	Administered Compound	Species/Strain	Age/Weight (g)	Sex/No.	Vehicle	LD_{50} (mg/kg bw)	LD_{50} (mg CN^-/kg bw)	Comment	Reference
s.c.	KCN	mouse/Swiss-Webster	NR/18-23	M/10/ group	saline	11.8 (10.6-13.2)	4.7 (4.2-5.3)	LD_{50} increased by pretreatment with sodium nitrite and sodium thiosulfate, enhanced by O_2.	Way et al., 1972
s.c.	KCN	mouse/NR	NR/18-32	F/10/ group	saline	6.02 ± 0.33	2.41 ± 0.12	At 23-25°C	Streicher, 1951
						2.86 ± 0.16	1.14 ± 0.06	At 4°C	
s.c.	NaCN	dog/NR	NR/NR	NR/16	NR	5.36 ± 0.28	2.84 ± 0.15	LD_{50} increased by immediate post-treatment administration of sodium thiosulfate, amyl nitrite, sodium nitrite and combinations of antidotes.	Chen and Rose, 1952
i.m.	HCN	rabbit/NR	adult/NR	M/10-15/ group	NR	1.50 (1.27-1.80)	1.44 (1.22-1.73)	Increased rate of breathing, vociferation, uncoordinated movement of head, ataxia, tremors, respiratory and cardiac arrest.	Ballantyne et al., 1971, 1972
				F/10-15/ group		0.95 (0.81-1.11)	0.91 (0.78-1.07)		
i.m.	KCN	rabbit/NR	adult/NR	M/10-15/ group	NR	3.06 (2.61-3.63)	1.22 (1.04-1.45)	Same as above, the rabbits lived longer following KCN rather than HCN administration.	Ballantyne et al., 1971, 1972
				F/10-15/ group		3.27 (2.70-4.08)	1.31 (1.08-1.63)		

NR - Not reported

s.c. = subcutaneous; i.p. = intraperitoneal; i.m. = intramuscular been administered intraperitoneally or subcutaneously to mice and dogs in order to determine the effects of antidotal treatment on the LD_{50} (Kruszyna et al., 1982; Way et al., 1966a, 1972; Isom and Way, 1973; Chen and Rose, 1952). Streicher (1951) demonstrated the effect of temperature on the toxicity of KCN. The LC_{50} for inhalation (not included in Table V-1) of HCN in Swiss-Webster mice for a 30-minute exposure and a 10-minute recovery period was determined to be 166 ppm (182.6 mg HCN/m^3) (Matijak-Schaper and Alarie, 1982).

Table V-2 is a summary of studies of acute toxicity other than LD_{50} determinations. For the purposes of this review, durations ranging from a single exposure up to 14 daily doses are considered to be acute. Time to death depends upon dose and rapidity of absorption. Three dogs receiving oral doses of KCN of 3.8, 10.7 and 20.3 mg KCN/kg bw (1.5, 4.3 and 8.1 mg CN^-/kg bw) died in 155, 21 and 8 minutes, respectively (Gettler and Baine, 1938). Oral doses of 10 and 15 mg KCN/kg bw (4 and 6 mg CN^-/kg bw) were fatal to rats and mice, respectively; the incidence of mortality depended on the amount administered (Ferguson, 1962). Basu (1983) found that an oral dose of 8 mg KCN/kg bw (3.2 mg CN^-/kg bw) resulted in no signs of toxicity in five guinea pigs, and slight tremors with complete recovery in three guinea pigs. This dose is approximately equal to the LD_{50} in mice (see Table V-1). Kreutler et al. (1978) studied the effect of KCN administered in the diet of rats in relation to protein content and iodine deficiency. The rats tolerated a much higher dose of cyanide (80 mg CN^-/kg bw/day) when it was mixed in the diet than when administered by gavage. All of the rats on the low protein diet lost body weight, regardless of other treatments. KCN-treated rats on a low protein diet deficient in iodine had

TABLE V-2

Acute Toxicity of Cyanides in Laboratory Animals

Route	Administered Compound	Species/ Strain	Age/ Weight (g)	Sex/No.	Vehicle	Dose/Concentration of Compound	Dose/Concentration as CN^-	Duration	Effects	Reference
Oral	KCN	dog/NR	NR/ 12.7 kg	NR/3	NR	3.8 mg/kg bw	1.5 mg/kg bw	single dose	death in 155 minutes	Gettler and Baine, 1938[a]
			NR/ 11.3 kg			10.7 mg/kg bw	4.3 mg/kg bw	single dose	death in 21 minutes	
			NR/ 11.9 kg			20.2 mg/kg bw	8.1 mg/kg bw	single dose	death in 8 minutes	
Oral	KCN	rat/ Sprague-Dawley	adult/NR	NR/20/ group	water	10 mg/kg bw	4.0 mg/kg bw	single dose	The compound was administered in volumes corresponding to % bw. At 1.35%, 10/20 rats died; at 2.5%, 14/20 died; at 5%, 19/20 died.	Ferguson, 1962
Oral	KCN	mouse/ Swiss-Webster	NR/NR	NR/20/ group	water	15 mg/kg bw	6.0 mg/kg bw	single dose	When administered in a volume corresponding to 1.25% bw, 7/20 died; at 2.5%, 15/20 died; at 5%, 19/20 died.	Ferguson, 1962
Oral	KCN	guinea pig/ Duncan-Hartley	NR/ 200-250	NR/8	sucrose	8 mg/kg bw	3.2 mg/kg bw	single dose	5 of the guinea pigs had no signs to toxicity after 30 min., 3 had slight tremors but recovered completely in 15 minutes.	Basu, 1983
Oral	KCN	rat/ Holtzman	NR/ 90-100 g	M/24	2% casein diet	0	0	14 days	Mean loss of bw = 30%	Kreutler et al., 1978
				M/14	2% casein diet	2000 mg/kg diet[a] (200 mg/kg bw/day)	800 mg/kg diet[a] (80 mg/kg bw/day)	14 days	Mean loss of bw = 31%; significantly increased mean absolute thyroid weight (~2x); mean thyroid-to-bw ratio (~2.5x) and plasma TSH (27x) compared with controls ($p<0.05$).	

TABLE V-2 (cont.)

Route	Administered Compound	Species/ Strain	Age/ Weight (g)	Sex/No.	Vehicle	Dose/Concentration of Compound	Dose/Concentration as CN⁻	Duration	Effects	Reference
Oral				M/14	2% casein diet + KI	2000 mg/kg diet (200 mg/kg bw/day)	800 mg/kg diet (80 mg/kg bw/day)	14 days	Mean loss of bw = 33%; mean absolute thyroid weight and mean plasma TSH were not significantly different from control. Thyroid-to-bw ratio was significantly decreased compared to control (~25% decrease), and compared with group without added KI to diet (~3.2x) ($p<0.05$).	Kreutler et al., 1978
				M/11	20% casein diet	0	0	14 days	Mean gain of bw = 37%. No significant change in absolute thyroid weight, thyroid-to-bw ratio or plasma TSH compared with 2% casein diet control.	
				M/10	20% casein diet	2000 mg/kg diet (200 mg/kg bw/day)	800 mg/kg diet (80 mg/kg bw/day)	14 days	Mean gain of bw = 41%. No significant change in absolute thyroid weight, thyroid-to-bw ratio, and plasma TSH compared with 20% casein diet control.	
Inhalation	HCN	dog/NR	NR/ 10.3 kg	NR/1	air	1.55 mg/kg bw^b	1.49 mg/kg bw^c	15 minutes	death	Gettler and Baine, 1938
			NR/ 9.1 kg	NR/1	air	1.11 mg/kg bw^b	1.07 mg/kg bw^c	10 minutes	death	
Inhalation	HCN	dog/ mongrels	adult/NR	NR/6	air	620 mg/m^3	595 mg/m^3	2.0 minutes	Died in ~16 hours, apneic	Haymaker et al., 1952
						590 mg/m^3	566 mg/m^3	2.0 minutes	Died in ~16 hours, apneic and comatose before death.	
						700 mg/m^3	672 mg/m^3	1.75 minutes	Died in 20 hours, apneic and comatose before death.	
						700 mg/m^3	672 mg/m^3	1.75 minutes	Prior to sacrifice at 24 hours, dog became comatose but recovered full consciousness.	

TABLE V-2 (cont.)

Route	Administered Compound	Species/ Strain	Age/ Weight (g)	Sex/No.	Vehicle	Dose/Concentration of Compound	Dose/Concentration as CN$^-$	Duration	Effects	Reference
Inhalation						165 mg/m^3	158 mg/m^3	10.0 minutes	Prior to sacrifice at 26 hours, dog became comatose but recovered; this dog received one ampule of amyl nitrate after gasing.	Haymaker et al., 1952
						690 mg/m^3	662 mg/m^3	2.0 minutes	Prior to sacrifice at 28 hours, dog became comatose but recovered.	
									4 of the dogs had convulsive seizures (individuals not specified). Histopathologic damage to gray matter of brain included necrosis of cerebral cortex, caudate nucleus and putamen, substantia nigra, globus pallidus, pulvinar of the thallamus and cerebellar cortex.	
Inhalation	HCN	rat/Long-Evans	adult/ 350	M/4/ group	air	0, 220 mg/m^3 (exposed 5 times)	0, 211 mg/m^3 (exposed 5 times)	one 12.5-minute exposure; 5 exposures with 4-day intervals between exposures	Increased activity of cardiac specific creatinine phosphokinase ~2-fold over control, was seen after each exposure but the increases at each exposure were not influenced by previous exposure; increased numbers of ectopic heart beats induced by norepinephrine ~8x above control; no consistent increase in incidence of histopathologic damage to myocardium. Pretreatment of rats with chlorpromazine-thiosulfate reduced the increase in plasma cardiac-specific creatine kinase activity and the number of ectopic beats induced by norepinephrine but increased the incidence of myocardial lesions.	O'Flaherty and Thomas, 1982

TABLE V-2 (cont.)

Route	Administered Compound	Species/ Strain	Age/ Weight (g)	Sex/No.	Vehicle	Dose/Concentration of Compound	Dose/Concentration as CN⁻	Duration	Effects	Reference
Dermal	HCN	dog/NR	NR/NR	NR/11	air	6500-16,900 mg/m³	6240-16,224 mg/m³	47-180 minutes	The heads of the dogs were excluded from the exposure chamber. No deaths were observed at 6500-10,900 mg HCN/m³ in 30 or 60 minutes. Respiration decreased and was labored and irregluar, face and throat twitches observed, deaths followed. Lungs were bright pink and collapsed.	Walton and Witherspoon, 1926
Dermal	HCN	guinea pig/NR	NR/NR	NR/8/ group	none	not quantified	NA	~8 minutes	The guinea pigs were prevented from inhaling vapors. A tube filled with liquid HCN was pressed against the abdomen. Signs of toxicity: rapid respiration, muscle twitches and convulsions began at 5-7 minutes, death at 7-8 minutes.	Walton and Witherspoon, 1926
i.p.	KCN	mouse/ Swiss-Webster	NR/NR	M/NR	water	0, 1, 2, 3, 4, 5 or 6 mg/kg bw	0, 0.4, 0.8, 1.2, 1.6, 2.0 or 2.4 mg/kg bw	single injection	Effects were rapid breathing, agitation, loss of coordination and convulsions. These signs were scarcely observed at 1 and 2 mg KCN/kg. At 3, 4 and 5 mg KCN/kg, there was gasping, irregular breathing and convulsions, beginning at 2-3 minutes. At 6 mg/kg, severe convulsions, cessation of breathing, death of 20% of the mice. At doses >6 mg KCN/kg, all died in 4 minutes. Changes corresponded to degree of inhibition of cytochrome oxidase.	Isom et al., 1982

TABLE V-2 (cont.)

Route	Administered Compound	Species/ Strain	Age/ Weight (g)	Sex/No.	Vehicle	Dose/Concentration of Compound	Dose/Concentration as CN^-	Duration	Effects	Reference
s.c.	NaCN	rat/ Wistar	adult/ 200-220	M/5-6/ group	saline	3 x 0 and 3 x 0.04 mg/kg bw	0.043 x 0 and 3 x 0.02 mg/kg bw	3 injections 10 minutes apart	The treated rats survived 5 hours; there was a significant increase in acetylcholinesterase activity ($p<0.05$) in cerebral cortex (57%), hippocampus (28%) and midbrain (18%) compared with controls ($p<0.05$).	Owasoyo and Iramain, 1980
i.v.	NaCN	dog/ mongrels	NR/15 kg	NR/NR	saline	1 mg/kg bw	0.5 mg/kg bw	single injection	EEG: lower brain electrical activity for 6 minutes, then depressed wave amplitude. EKG: sinus pause, bradycardia (slow heart rate), elevated T or biphasic T wave. Initial decrease followed by marked increase in systolic, diastolic and venous blood pressure for 10 minutes, returned to pre-NaCN level in 20-30 minutes. There was hyper- followed by hypoventilation.	Burrows et al., 1973

[a] Confusion in reference in which KCN was the compound administered as described in text, and HCN was the compound referred to in table.

[b] Dose in mg/kg bw was experimentally determined.

[c] Dose in mg/kg/day was calculated from dietary concentration on the assumption that a young growing rat consumes a quantity of food equal to 10% of its bw/day.

NR = Not reported

TSH = Thyroid stimulating hormone

KI = Potassium iodide

increased thyroid weight, increased thyroid-to-body weight ratio and increased levels of plasma thyroid stimulating hormone (TSH). Addition of iodine to the diet protected the rats from the effects on the thyroid. Rats on high protein diets gained body weight regardless of treatment. Although these diets were not supplemented by iodine, no effect of cyanide on the thyroid were observed. Ingestion of cyanogen glycoside-containing foods, along with nutritional deficiencies, is suspected of having a goitrogenic effect in humans (Ermans et al., 1972) (see Oral Subchronic and Chronic Exposure Section in Chapter VI).

Effects of acute inhalation exposure of dogs and rats to HCN are also summarized in Table V-2. A dog receiving a bolus of 1.5 mg CN^-/kg bw by gavage died in 155 minutes, while a dog inhaling a total of 1.5 mg CN^-/kg bw died in 15 minutes (Gettler and Baine, 1938). Correlation of duration of exposure and concentration with effect is difficult because some animals recover from exposures that are fatal to others, even within the same species. This phenomenon was demonstrated in dogs by Haymaker et al. (1952) (see Table V-2). Histopathologic lesions to the gray matter of the brain were observed when the dogs were necropsied. Moss et al. (1951) reported a minimum lethal concentration of 55 mg HCN/m³ for $\leq$20 minutes in female rats. Rats tolerated repeated acute inhalation exposures (one 12.5-minute exposure every 4 days) to HCN of 220 mg/m³ (O'Flaherty and Thomas, 1982). During the experimental period, the rats had increased activities of cardiac specific creatine phosphokinase (an index of myocardial damage) and increased numbers of ectopic heart beats in response to norepinephrine. The rats were killed and necropsied within 2 weeks of the last exposure. No consistent increase in incidence of lesions to the myocardium was observed.

Barcroft (1931) compared the sensitivities of a variety of species to inhaled HCN with respect to the amount of time it took the animals to die while inhaling a concentration of 1000 mg/m³. The results are presented in Table V-3. The species were also compared with respect to the highest concentration that the animals could breathe "indefinitely." It was not clear as to how this determination was made, but the reported concentrations ranged from 100-400 mg HCN/m³. The order of sensitivities to these nonlethal concentrations, from the most sensitive to the least sensitive species was dog = rat > mouse > rabbit = monkey = cat > goat > guinea pig.

Toxic effects of the cyanides administered by other routes are included in Table V-2. Dermal absorption of HCN gas resulted in death in dogs and guinea pigs (Walton and Witherspoon, 1926). A dose-response for single doses of KCN administered intraperitoneally to mice was defined by Isom et al. (1982). Such signs as rapid breathing, agitation, loss of coordination and convulsions were rare at doses of 1 and 2 mg KCN/kg bw (0.4 and 0.8 mg CN^-/kg bw). At 3, 4 and 5 mg KCN/kg bw (1.2, 1.6 and 2.0 mg CN^-/kg bw), these effects were observed within 2-3 minutes. At 6 mg KCN/kg bw (2.4 mg CN^-/kg bw), there was 20% mortality in 4 minutes. Subcutaneous administration of NaCN to rats resulted in significantly increased acetylcholinesterase activity in the cerebral cortex, hippocampus and midbrain compared with controls (Owasoyo and Iramain, 1980). Intravenous administration of 1 mg NaCN/kg bw (0.5 mg CN^-/kg bw) to dogs resulted in EEG, EKG and blood pressure changes (Burrows et al., 1973).

TABLE V-3

Sensitivity of Various Species to Inhalation Exposures of HCN*

Species (number/species not given)	Lethal time of exposure to a Concentration of 1000 mg HCN/m^3 (minutes)
Dog	0.8
Mouse	1.0
Cat	1.0
Rabbit	1.0
Rat	2.0
Guinea pig	2.0
Goat	3.0
Monkey	3.5

*Source: Barcroft, 1931

Subchronic Exposure. Details of the studies on the effects of subchronic exposure of animals to cyanides are provided in Table V-4. (As mentioned previously in the Acute Exposure Section, animals can tolerate higher doses of cyanides when the compounds are administered in the diet.) Rats tolerated 25 daily doses of KCN, each of which were equal to the acute oral LD_{50} (10 mg KCN/kg bw or 4 mg CN^-/kg bw), when the chemical was mixed in the diet (Hayes, 1967). Indeed, 90 daily doses that were equal to 25 times the LD_{50} did not result in mortality when administered in the diet. Rats tolerated a higher oral dose of KCN (~30 mg KCN/kg bw/day or 12 mg CN^-/kg bw/day for 21 days) that was administered in drinking water (Palmer and Olson, 1979), than when KCN was administered in a bolus by gavage with water as the vehicle (Hayes, 1967; Gaines, 1969). The intermittent ingestion of low doses over a day, would allow for sufficient detoxification to account for the sublethal effects. The rats that had received KCN in the drinking water had significantly increased liver weights when compared with controls (Palmer and Olson, 1979). Other parameters were not examined, since the study was designed to determine the effect of cyanide on selenite toxicity. KCN in drinking water prevented chronic selenosis; however, KCN in the diet did not. Rats receiving KCN in the diet for 21 days (20 mg KCN/kg bw/day or 8 mg CN^-/kg bw/day) did not have increased liver weights, but the doses were lower than when KCN was added to the drinking water.

Tewe (1982) studied the effects of dietary KCN, administered for 84 days, in the African giant rat. The concentration in the diet (2500 mg KCN/kg diet) was approximately equivalent to 90 mg KCN/kg bw/day (36 mg CN^-/kg bw/day). This was the same dose tolerated by Sherman rats for 90 days (Hayes, 1967). The effects in the African giant rat were slightly

TABLE V-4

Effects of Subchronic Exposure of Laboratory Animals to Cyanide

Route	Administered Compound	Species/ Strain	Age/ Weight	Sex/No.	Vehicle	Dose/Concentration of Compound	Dose/concentration as CN⁻	Duration	Effects	Reference
Oral	KCN	rat/Sprague-Dawley	NR/70 g	M/7/ group	drinking water	0 and 200 mg/ℓ^{a} (30 mg/kg bw/day)	0 and 80 mg/ℓ^{a} (12 mg/kg bw/day)	21 days	Increased liver weight of treated animals (15.8 g) compared with controls (13.5 g), $p<0.05$. No effect on bw gain.	Palmer and Olson, 1979
Oral	KCN	rat/Sprague-Dawley	NR/70 g	M/7/ group	diet	0 and 200 mg/kg^{b} diet (20 mg/kg bw/day)	0 and 80 mg/kg^{b} diet (8 mg/kg bw/day)	21 days	No increase in liver weight of treated animals (13.7 g) compared with controls (13.5 g). No effect on bw gain.	Palmer and Olson, 1979
Oral	KCN	rat/Sherman	adult/NR	M/NR	diet	0, 10 mg/kg bw/day	0, 4 mg/kg bw/day	25 days	No mortality; this dose is equal to the 1-day oral LD_{50} of KCN in the same strain of rats; however, the rats tolerated the dose when mixed in feed.	Hayes, 1967
Oral	KCN	rat/Sherman	adult/NR	M/NR	diet	0-250 mg/kg bw/day	1-100 mg/kg bw/day	90 days	No mortality. The rats tolerated the doses, which were up to 25x the acute oral LD_{50} when mixed in the diet.	Hayes, 1967
Oral	KCN	rat/Sprague-Dawley	weanling/ NR	M+F/8/ group	diet	0 and 1875 mg/kg diet	0 and 750 mg/kg diet	56 days	No significant difference in food consumption, bw gain, food efficiency, protein efficiency ratio and liver and kidney to bw ratio.	Tewe and Maner, 1982
Oral	KCN	rat/ Chicetomys Waterhouse (African giant rat)	weanling/ ~90 g	M/6/ group F/2/	diet	0 and 2500^{c} mg/kg diet (90 mg/kg bw/day)	0 and 1000^{c} mg/kg diet (36 mg/kg bw/day)	84 days	Slightly reduced feed consumption and bw gain of treated animals compared with controls. No histopathologic changes in thyroid, kidney, liver or spleen.	Tewe, 1982

TABLE V-4 (cont.)

Route	Administered Compound	Species/ Strain	Age/ Weight	Sex/No.	Vehicle	Dose/Concentration of Compound	Dose/concentration as CN⁻	Duration	Effects	Reference
Oral	KCN	pig/ Yorkshire	weanling/ NR	M + F	diet	0 and 1250[c] mg/kg diet	0 and 500[c] mg/kg diet	56 days	A small but significant reduction in average food consumption ($p<0.05$), but no significant difference in bw gain between treated and control pigs. No significant difference in food efficiency, protein efficiency ratio, organ to bw ratios of thyroid, liver, kidney, spleen or heart. No histopathologic changes.	Tewe and Maner, 1980
Oral	NaCN	dog/beagle	6.5 months/ Mean-7.1 kg at start and mean 8.1 kg at end of test	1M, 1F control, 3M, 2F treated	diet	0 and 2500[d] mg/kg diet (6 mg/kg bw/day)	0 and 1000[d] mg/kg diet (3 mg/kg bw/day)	30-32 days	No effect on food consumption or bw gain, no effect on hemoglobin concentration, hematocrit or differential white cell count. Complete autopsies and comprehensive histological examinations revealed no effect on organ to bw ratios and no treatment-related gross or histopathologic lesions.	American Cyanamid Co., 1959
Oral	NaCN	dog/NR	NR/NR	NR/1 control, 3 treated	capsule	0, 0.5, 1.0 up to 2 x 2.0 mg/kg bw/day (6 mg/kg bw day)	0, 0.27, 0.53 up to 2 x 1.1 mg/kg bw/day (3 mg/kg bw/day)	15 months	At >1.0 mg NaCN/kg bw, acute signs of toxicity were observed immediately after dosing, but recovery occurred in <0.5 hours. No pathologic changes in organs or metabolic systems, but erythrocyte count was increased and serum albumin decreased. Degenerative changes in ganglion cells of CNS and especially Purkinje cells of cerebellum (necrosis, reduced RNA content, inflammation) in all treated dogs.	Hertting et al., 1960

TABLE V-4 (cont.)

Route	Administered Compound	Species/ Strain	Age/ Weight	Sex/No.	Vehicle	Dose/Concentration of Compound	Dose/concentration as CN^-	Duration	Effects	Reference
Inhalation	HCN	rabbit/ Danish	NR/2.0-2.5 kg	M/22/ group	air	0, 0.55 mg/m^3	0, 0.53 mg/m^3	28 days	No significant difference between control and treated animals with respect to ultrastructural changes in myocardium.	Hugod, 1981
s.c.	NaCN	rat/Charles River	adult/ 200-350 g	M/221	saline	0 and TWA^a doses of 1.16, 2.40 and 3.24 mg/kg bw/day	0 and TWA^a doses of 0.61, 1.31 and 1.72 mg/kg/day	3 days a week for 3 months (90 days)	There was high mortality in all treated groups: 159/208 treated rats died before the end of the experiment; 107 died in the first 3 weeks. In 15 minutes after each injection most rats became comatose, but recovered. Many appeared blind and ataxic before death and had necrotic lesions of corpus callosum and optic nerve on autopsy. Severely affected rats had focal constriction of optic nerve. A no-effect level was 0.20 mg/kg bw/day TWA dose of NaCN (0.11 mg CN^-/kg bw/day) for 90 days.	Lessell, 1971
s.c.	KCN	rat/Wistar	adult/NR	NR/3/ group	NR	0 and 0.5 mg/rat (1.43 mg/kg bw/^{f} injection)	0.2 mg/rat (0.57 mg/kg bw/^{f} injection)	once weekly for 22 weeks	Treated rats had degenerating cells in cortex, degenerating Purkinje cells in cerebellum and hippocampus; degenerating neurons in brain; pallor in myelin of corpus callosum; decreased vitamin B_{12} levels in liver.	Smith et al., 1963

TABLE V-4 (cont.)

Route	Administered Compound	Species/ Strain	Age/ Weight	Sex/No.	Vehicle	Dose/Concentration of Compound	Dose/concentration as CN⁻	Duration	Effects	Reference
s.c.	KCN	baboon/ *Papio cynocephalus* and *P. anubis*	9 months/ 3.7 kg	M/7 M/10	phosphate buffer and adrenalin	0 1 mg/kg bw, 5 days/week	0 0.4 mg/kg bw, 5 days/week	42 months	Rise in hemoglobin ($p<0.01$), low mean erythrocyte volume ($p<0.01$), decreased mean erythrocyte hemoglobin content ($p<0.01$) from pre-test determination.	Crampton et al., 1979
i.m.	KCN	monkey/ rhesus	NR/2.5-5.0 kg	NR/25	water	TWA dose[e] 1.9-38 mg/kg/day	TWA 0.76-15.2[e] mg/kg bw/day	17-103 days	All treatments were fatal in <2 hours to 13 days after the last dose; 10 monkeys had lesions in white matter (cell proliferation, demyelination necrosis), 13 had lesions of gray matter (minor damage and necrosis). It was not possible to correlate dose with effect.	Hurst, 1940

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[a] The dose in mg/kg bw/day was calculated from the concentration in drinking water, assuming that a young rat consumes an amount of water equal to ~15% of its bw per day.

[b] The dose in mg/kg bw/day was calculated from the concentration in food, assuming that a young growing rat consumes an amount of food equal to ~10% of its bw per day.

[c] The dose in mg/kg bw/day was calculated from food consumption and body weight information supplied in the report.

[d] The doses were calculated from data supplied in the method of meal preparation on the quantity of NaCN (45 mg) mixed with each meal. The dogs consumed all the meals, and the average weight of the dogs during the test was 7.6 kg. The concentration of NaCN in the meal was 500 mg/kg meal.

[e] TWA (time-weighted average) doses were calculated. In the study, the doses were raised throughout the experiment; the investigator supplied cumulative doses, and these cumulative doses were divided by 90 days to give the TWA doses.

[f] The dose in mg/kg bw was calculated by assuming the the average weight of a rat is 0.35 kg.

reduced food consumption, slightly reduced body weight gain and an increase in serum urea. The differences from control were significant only for serum urea. The brain was not examined histologically, although it is a target organ for subcutaneously administered cyanide in rats (Smith et al., 1963; Lessell, 1971).

Tewe and Maner (1980, 1982) conducted studies in pigs and rats to determine the interrelationships of cyanide, dietary protein and iodine on the physiologic performance. Only those portions of the reports where pigs and rats were maintained on standard diets with or without KCN are discussed here. There were no significant differences between rats (750 ppm CN^- in diet for 56 days) and controls when compared for food consumption, body weight gain, food efficiency (food intake/body weight gain), protein efficiency ratio (body weight gain/protein intake) and liver and kidney weight-to-body weight ratios (Tewe and Maner, 1982). Histologic examinations were not performed. Treated pigs (500 ppm CN^-) had slightly reduced food consumption; however, body weight gain was not affected (Tewe and Maner, 1980). Histologic examination of the pigs revealed no pathologic changes in thyroid, hypophysis, stomach, liver, cardiovascular tissue, spleen, tonsils, thymus, intestinal mesentery, kidney, eye, brain, spinal cord, neural ganglia or bone. Organ-to-body weight ratios of thyroid, liver, kidney, spleen and heart were not different from controls.

The American Cyanamid Co. (1959) conducted a study in beagles on the effects of NaCN mixed with their food. The dogs consumed 3 mg CN^-/kg bw/day for 30-32 days. There were no clinical signs of toxicity or effects on food consumption, body weight gain or hematologic parameters. Histological examination was extensive and included tongue, tonsils, cervical lymph node, salivary gland, thyroid, trachea, myocardium, aorta, lung, thymus, liver, gall bladder, pancreas, esophagus, stomach, duodenum, jejunum, ileum, colon, caecum, rectum, mesenteric lymph node, spleen, adrenal, kidney, ureter, urinary bladder, skeletal muscle, cerebellum, cerebrum, spinal cord, pituitary, testis, prostate, ovary, uterus and vagina. No treatment-related abnormalities were found. There were no differences in organ-to-body weight ratios of submaxillary glands, thyroid, heart, lung, liver, adrenal, pancreas, spleen, kidney, brain, pituitary, testis or ovary. The dose had been chosen on the basis of the concentration of NaCN in the food that the dogs would accept and eat completely. Dogs receiving doses of >1.0 mg NaCN/kg bw/day (0.5 mg CN^-/kg bw/day) for up to 15 months had signs of intoxication immediately after each dosing, but they recovered in <0.5 hour (Hertting et al., 1960). The NaCN was administered in a capsule. Degenerative changes in ganglion cells of the CNS were observed in all three treated dogs. The lowest exposure was 0.27 mg CN^-/kg bw/day.

Effects of subchronic exposure to cyanide by other routes are included in Table V-4. Rabbits exposed to 0.55 mg HCN/m^3 air for 28 days had no treatment-related changes in the ultrastructure of the myocardium (Hugod, 1981). Rats treated subcutaneously with NaCN in TWA (time-weighted average) doses of 0.61, 1.31 and 1.72 mg CN^-/kg bw/day over 90 days had high rates of mortality and histopathologic damage to the brain (Lessell, 1971). The damage consisted of necrotic lesions in the corpus callosum and the optic nerve. A no-effect level was a TWA dose of 0.11 mg CN^-/kg bw/day for 90 days. Smith et al. (1963) also found histopathologic damage to the brains of rats treated once weekly for 22 weeks with subcutaneous injections of 0.57 mg CN^-/kg bw. Hurst (1940) found necrotic lesions in white and gray matter of the brains of rhesus monkeys treated with lethal intramuscular doses of KCN (0.76-15.2 mg CN^-/kg bw/day). Baboons treated subcutaneously for 42 months with 1 mg NaCN/kg bw (0.4 mg CN^-/kg bw) 5 days/week had differences in hematologic parameters compared with controls (Crampton et al., 1979). There was no difference in body weight gain, and the treated animals appeared to be in good health throughout the experiment.

Chronic Exposure. Only two studies were encountered that provided information on the effects of long-term exposure of animals to cyanide. Details of the studies are presented in Table V-5.

In the study of Howard and Hanzal (1955), groups of 10 male and 10 female Carworth Farms rats were maintained for 104 weeks on diets that had been fumigated with HCN. It was necessary to measure the loss of HCN due to evaporation from the chow and to prepare fresh rations every other day to nominal concentrations of 100 and 300 mg HCN/kg diet. Results of the analysis of residues over the 2-year duration of the study indicated an average drop in the dietary concentration of HCN over 2 days from 100 mg/kg diet to 51.9 mg/kg diet for the low-dose level and from 300 mg/kg diet to 80.1 mg/kg diet for the high-dose level. Thus, the average concentrations are 76 mg/kg diet for the low-dose level and 190 mg/kg diet for the high-dose level.

TABLE V-5

Effects of Chronic Exposure of Laboratory Animals to Cyanide

Administered Compound	Species/ Strain	Age/ Weight	Sex/No.	Vehicle	Dose/Concentration of Compound	Dose/Concentration as CN^-	Duration	Effects	Reference
HCN	rat/ Carworth Farms	weanling/ ~57 g	M/10/ group	diet	0, 76 and 190[a] mg/kg diet (0, 3.3 and 8.1 mg/kg bw/day)	0, 73 and 183[a] mg/kg diet (0, 3.2 and 7.8 mg/kg bw/day)	104 weeks	No effect on growth rate, no signs of toxicity, no histopathologic changes in heart, lungs, liver, spleen, stomach, small and large intestines, kidney, adrenals, thyroid, testes, uterus, ovary and the cerebrum and cerebellum of the brain.	Howard and Hanzal, 1955
			F/10/ group		(1, 4.5 and 10.8 mg/kg bw/day)	(0, 4.3 and 10.4 mg/kg bw/day)			
KCN	rat/NR	weanling/ 43 g	M/10/ group	diet	0, 1500 mg/kg[b] diet (75 mg/kg bw/day)	0, 600 mg/kg[b] diet 30 mg/kg bw/day)	11.5 months	No deaths or clinical signs. Significantly (no p values) reduced bw gain, increased excretion of thiocyanate at 4 months and at at 11 months, decreased plasma thyroxine levels, decreased secretion rates at 4 months. No effect on plasma thyroxine at 11 months, no definitive lesion to sciatic, thyroid, optic or CNS tissue. Vacuoles and accumulation of fluid in spinal cord white matter with moderate primary myelin degeneration were observed in treated rats. These changes were more pronounced in KCN-treated rats that were maintained on methionine and vitamin B_{12} deficient diets.	Philbrick et al., 1979

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[a] The doses in mg/kg bw/day were calculated using data on food consumption and bw supplied in the report.

[b] The dose in mg/kg bw/day was calculated assuming that a rat consumes an amount of feed equal to 5% of its body weight/day.

NR = Not reported

During the 2 years of this study, the growth curves for all groups did not vary as a result of treatment. Food consumption, hematologic values and survival were also similar in all groups during the 2 years. At termination of the study, the only pathologic lesions observed were those associated with aging. The only effects of treatment were increased CN^- level in the red blood cells, and increased thiocyanate levels in the plasma, red blood cells, liver and kidneys of animals from both treatment groups.

Philbrick et al. (1979) mixed KCN in the diet at a concentration of 1500 mg/kg diet and maintained groups of 10 male weanling rats (strain not specified) on this diet for 11.5 months. When expressed in terms of cyanide, this dietary concentration is higher than the concentration of cyanide in the food of the rats in the Howard and Hanzal (1955) study. One group of animals (the + control) received a diet containing 10% casein supplemented with 0.3% DL-methionine, KI and vitamin B_{12}. Two groups received this diet plus either 1500 ppm KCN or 2240 KSCN. Another group (the - control) received the 10% casein diet with no added KI or vitamin B_{12}. Two additional groups received this - control diet plus either 1500 ppm·KCN or 2240 ppm KSCN. Thus, of those two groups receiving KCN, one received a complete diet whereas the other was restricted in iodine and vitamin B_{12}. No deaths occurred nor were there any gross signs of toxicity. Effects were reduced body weight gain, decreased plasma thyroxine levels and decreased rate of thyroxine secretion. The effects appeared greater in the animals on the deficient diet, although the difference was not always significant. There were no definitive histopathologic lesions in the optic or CNS tissue, thyroid or sciatic tissue; however, vacuolization and myelin degeneration were observed in spinal cord sections.

Target Organ Toxicity

Central Nervous System. Several studies discussed in the General Toxicity Section described histopathologic damage to brain tissues. Haymaker et al. (1952) found lesions in the gray matter of brains of dogs after fatal inhalation exposure to HCN. The damage includes necrosis of the cerebral cortex, caudate nucleus and putamen, substantia nigra, globus pallidus, pulvinar of the thallamus and cerebellum cortex. Dogs given subchronic oral doses of NaCN had degenerative changes in ganglion cells, especially Purkinje cells of the cerebellum (Hertting et al., 1960). EEG changes such as low electrical activity and depressed wave amplitude were observed in dogs given NaCN intravenously (Burrows et al., 1973).

The brain is also a target organ in rats. Smith et al. (1963) found that subcutaneous administration of KCN to rats resulted in degeneration of pyramidal cells in the cerebral cortex, degeneration of the cerebellum (Purkinje cells) and hippocampus, degenerating neurons in the brain and pallor of myelin in the corpus callosum. Lessell (1971) described necrotic lesions in the corpus callosum and optic nerves of rats treated subcutaneously with NaCN. Focal constriction of the optic nerve was observed in severely affected rats. In a subsequent study, in which the doses of NaCN were adjusted in order to keep rats in a coma for 225-260 minutes, there were severe ultrastructural pathologic changes in the optic nerve, particularly in the retrobulbar zone (Lessell and Kuwabara, 1974). The optic nerve lesions included edema, enlarged astrocytes, clumping of myelin, nerve fiber degeneration and necrotic and swollen axons that had few microtubules. Owasoyo and Iramain (1980) found increased activity of acetylcholinesterase in the cerebral cortex, hippocampus and midbrain of rats given subcutaneous doses of NaCN. Ferraro (1933) studied the CNS histopathology of cats and monkeys given increasing doses of KCN. The damage included demyelination in white matter of the frontal, occipital, parietal and temporal lobes, the corpus callosum, the cerebellum, the spinal cord and optic nerve. Degeneration of axis cylinder, gliosis, hypertrophy and vacuolization of oligodendroglia were also observed.

Heart. O'Flaherty and Thomas (1982) found that inhalation of HCN by rats resulted in increased activity of plasma cardiac specific creatine phosphokinase, an indicator of myocardial damage, although there was no consistent increase in the incidence of lesions to the myocardium. Hugod (1981) also failed to detect changes in the ultrastructure of the myocardium of rabbits after HCN inhalation. EKG changes following intravenous injections of NaCN in dogs included sinus pause, bradycardia and elevated or biphasic T waves (Burrows et al., 1973). There was also a marked increase in systolic, diastolic and venous blood pressures.

Thyroid. The thyroid may be a target organ for the cyanides through the formation of thiocyanate, which inhibits the uptake of iodine (Ermans et al., 1972). Kreutler et al. (1978) found that the effect of 14-day orally administered KCN (2000 ppm in the diet) on the thyroid weights and plasma levels of TSH in rats was inhibited by addition of iodine to the diet. However, Philbrick et al. (1979) reported decreased thyroxine levels and decreased rates of thyroxine secretion in rats treated chronically with standard diets containing KCN.

Other Effects

Carcinogenicity. Pertinent data regarding the carcinogenicity of HCN, KCN and NaCN were not located in the available literature, and these chemicals are not scheduled for testing by the National Toxicology Testing Programs (NTP, 1983). Perry (1935) found that inhalation exposure of rats to hydrogen cyanide retarded the growth of implanted Jensen rat sarcomas, but effective concentrations were very near the lethal concentrations. Brown et al. (1960) found that intraperitoneal injections of cyanide prolonged the lives of mice with transplanted Ehrlich ascites tumors and Sarcoma 180. Human patients with advanced cancers in the pelvic region tolerated pelvic perfusions of cyanide without evidence of toxicity. Other studies on the anti-tumor activity of cyanide and the controversial cyanogenic glycoside, amygdalin (laetrile), which releases cyanide on enzymatic hydrolysis, have been reviewed elsewhere (U.S. EPA, 1978).

Mutagenicity. Most of the assays of cyanides for mutagenicity and effects on DNA synthesis have been negative. De Flora (1981) found that KCN was negative for reverse mutation in *Salmonella typhimurium* strains TA1535, TA1537, TA1538, TA98 and TA100, using both the spot test and plate incorporation application technique, up to a dose of 3x10 nmoles/plate. This was the highest dose tested due to bacterial toxicity. Addition of the S-9 mix, prepared from livers of Aroclor-induced rats, had no effect on the response. More recently, Kushi (1983) reported that HCN gas was marginally mutagenic to *S. typhimurium* strain TA100 in doses up to 5 mg/plate. Addition of S-9 mix decreased the mutagenic response. Negative results were obtained in strain TA98. Karube et al. (1981) tested cyanide, a known inhibitor of cellular respiration (see Chapter VII), by a method employing the rec assay in Bacillus subtilis strains M45 Rec$^-$ and H17 Rec$^+$. The technique involved the use of two microbial electrodes consisting of immobilized bacteria on oxygen electrodes to measure the preferential death of the Rec$^-$ strain in response to decreased respiration by the DNA-damaged bacteria. If the test chemical damaged the DNA, then the Rec$^+$ strain could repair the damage, and the rate of current increase at the Rec$^+$ electrode would be slower than at the electrode of the repair-deficient Rec$^-$ strain. Cyanide increased the rate of current at both electrodes equally (dose-related), since the inhibition of cytochrome oxidase, rather than DNA damage, was responsible for the decrease in cellular respiration (see Chapter VII).

Teratogenicity and Other Reproductive Effects. Doherty et al. (1982) studied the teratogenicity of NaCN in pregnant Golden Syrian hamsters. On day 6 of gestation, osmotic minipumps were implanted subcutaneously at the back of the necks of 5-7 animals/group. The pumps delivered doses of NaCN of 0, 0.126, 0.1275 or 0.1295 mmoles/kg bw/hour (0, 148.2, 149.9 or 152.3 mg NaCN/kg bw/day or 78.5, 79.4 or 80.7 mg CN$^-$/kg bw/day) from days 6-9 of gestation, at which time the pumps were removed. The hamsters were killed on day 11 of gestation. The osmotic minipump method of administration was chosen in order to approximate the slow release of cyanide from nitriles during in vivo metabolism. It was believed that the teratogenic effect of nitriles and cyanogenic glycosides, e.g., laetrile (Willhite et al., 1981; Willhite, 1982, 1983) was due to in vivo release of cyanide. The results are presented in Table V-6. Severe teratogenic effects were observed at all three doses. Preliminary experiments revealed that a dose of 0.126 mmole/kg/hour (148.0 mg/kg/day) resulted in no fetal abnormalities, while a dose

TABLE V-6

Fetotoxic and Teratogenic Effects of NaCN in Hamsters[a]

	Treatment[b]			
		NaCN (mg/kg bw/day)[c]		
	Distilled Water (1.7 μl/hour)	148.2	149.9	152.3
Litters	6	5	6	6
Maternal bw change g ± SD	-4 ± 5	-16 ± 9	-13 ± 10	-16 ± 12
Litters completely absorbed	0	2	3	5
Total resorptions/ total implantations (%)	8/83 (10)	44/70 (63)[d]	60/83 (72)[d]	72/87 (83)[d]
Number litters[e] affected (%)	3 (50)	2 (67)	3 (100)	1 (100)
Total malformed total number live fetuses (%)	4/75 (5)	16/26 (62)[d]	10/23 (43)[d]	1/15 (7)[f]

TABLE V-6 (cont.)

	Treatment[b]			
		NaCN (mg/kg bw/day)[c]		
	Distilled Water (1.7 μℓ/hour)	148.2	149.9	152.3
Abnormalities in live fetuses				
neural tube[g]	0	16	6	1
heart	0	0	4	0
limb or tail	3	0	4	0
other[h]	1	0	1	0
Crown-rump length, mm ± SD	8.19 ± 0.54	3.33 ± 0.29[f]	6.61 ± 1.64[d]	NR

[a] Source: Doherty et al., 1982

[b] The NaCN was delivered by osmotic minipumps implanted subcutaneously.

[c] The doses correspond to rates of 0.126, 0.1275 and 0.1295 mmole/kg/hour.

[d] Significantly different from control ($p<0.05$).

[e] Litters affected of those litters with one or more live fetuses.

[f] Not included in statistical analysis, too few fetuses.

[g] Includes exencephaly, encephalocoele and nonclosure.

[h] Includes microphthalmia and one fetus with a small caudal half.

NR = Not reported

of 0.133 mmole/kg/hour (156.4 mg/kg/day) resulted in 100% resorptions and death to some of the dams. In addition, mild toxicity was observed at 148.2 and 149.9 mg/kg/day, and more severe effects were seen at 152.3 mg/kg day. Toxic signs included shortness of breath, incoordination, reduced body temperature and loss of body weight. In experiments with pair-fed controls, it was shown that the loss of body weight, in itself, was not related to the fetal abnormalities. No significant relationship between maternal toxicity and the incidence of fetal malformations was found by analysis of variance of the transformed data ($p>0.05$). When thiosulfate was co-administered with cyanide, no teratogenic effect was found. The investigators stated that the results do not imply a dose-response relationship because the variability in certified pump rates of individual minipumps is larger than the percentage difference among doses. Furthermore, the pumping rates cannot be verified in vivo.

Tewe and Maner (1981a) studied the effect of KCN added at a concentration of 500 ppm as the cyanide ion (500 mg CN^-/kg diet or 1250 mg KCN/kg diet) to a basal diet containing low-HCN cassava (21 mg HCN/kg) meal on the reproductive performance of female Wistar rats. Control rats were fed the basal diet (which contained 12 mg HCN/kg diet) in quantities that were equal to the diet consumed by treated rats. The KCN-treated rats were fed the test diet from 19.7±1.8 days before pregnancy, through lactation and during the post-weaning period. The controls were fed the control diet from 16.3±1.1 days before pregnancy and through post-weaning. Male rats did not receive the diets. Prior to parturition, the pregnant rats were separated, so that half the treated dams would remain on the test diet, the other half on the basal diet. Controls were separated similarly. At weaning, two rats from each litter were selected and assigned at random to control and treatment groups. No significant differences were found among the various treated and control groups with respect to weight gain during gestation, litter size, birth weight of pups, feed consumption and body weight change during lactation, weights of maternal liver and kidney, weanling weights or mortality of offspring. The offspring that were continued on the diets during the post-weaning period consumed significantly less food and grew at a significantly slower rate than the basal diet offspring, regardless of previous cyanide exposure (_in utero_ and/or in milk and/or in diet). The protein efficiency ratio of rats exposed _in utero_ and fed cyanide during the post-weaning phase and was significantly reduced compared with basal diet rats.

In a similar study, Tewe and Maner (1981b) studied the effect of cyanide on the reproductive performance of pregnant Yorkshire pigs. Cassava (containing a low level of HCN) was supplemented with protein, minerals and vitamin mix to which was added KCN. The groups, consisting of six pigs each, received basal diet of low cyanide (30.3 mg CN^-/kg diet) or the basal diet plus cyanide which provided total CN^- levels of 276.6 and 520.7 mg CN^-/kg diet. The concentrations as mg CN^-/kg diet were calculated by the investigators. The diets were started on the day after breeding and continued until parturition. Two pregnant pigs/group were killed on day 110 of gestation; the remaining pigs were fed their respective diets until parturition and then fed standard diets (no cyanide) during the 56 days of lactation. The piglets were not fed any cyanide. No differences were found with respect to litter size, litter size at weaning, birth weight of piglets, daily feed intake of sows or piglets. In the pigs that were killed on day 110 of gestation, no significant differences were found among groups for body weight, body weight gain during gestation, organ-to-body weight ratios of thyroid, spleen, liver, kidney and heart, number of fetuses/litter, weight of fetuses, weight of fetal liver or kidney. The thyroid-to-body weight ratios of fetuses from sows receiving 276.6 mg CN^-/kg diet were significantly reduced ($p<0.05$) compared with the low-cyanide group (30.3 mg CN^-/kg diet), but the high-cyanide (520.7 mg CN^-/kg diet) group was not different from the low-cyanide group. Fetal spleen-to-body weight ratio was significantly reduced ($p<0.05$) in the high-cyanide group compared with both other groups. The fetal heart-to-body weight ratio of high-cyanide group was significantly reduced ($p<0.05$) compared with the low-cyanide group. Histopathologic examination of two killed pigs/group on day 110 of gestation indicated hyperplasia of kidney glomerular cells in one sow from each of the low- and medium-cyanide groups and in both sows of the high-cyanide group. Both high-cyanide sows had an accumulation of colloid and follicular cells of low height in the thyroid. No difference in hypophysis, adrenal, pancreas, tongue, esophagus, stomach, liver, cardiovascular tissues, lymphoreticular system of the spleen, tonsils, thymus, intestinal mesenteries, eye, brain or spinal cord were observed between the treatment groups.

Summary

Signs of acute poisoning by cyanide include rapid breathing, gasping, tremors, convulsions and death (Di Palma, 1971). The speed of onset and the severity of the effects depend upon the route, the dose, the duration of exposure and the compound administered. Inhalation of HCN results in fastest absorption and appearance of toxic signs. Gastrointestinal absorption of the cyanide salts results in passage into the liver, the major site of detoxification. Cyanide exposure results in death because the cyanide ion reacts with cytochrome oxidase, blocking cellular respiration. If enough cyanide is detoxified before death occurs, the animal may recover.

The acute oral LD_{50} for KCN was 10 mg/kg bw (4 mg CN^-/kg bw) in rats (Gaines, 1969; Hayes, 1967) and 8.5 mg KCN/kg bw (3.4 mg CN^-/kg bw) in mice (Sheehy and Way, 1968). Intraperitoneal injection of NaCN in mice results in a similar LD_{50} as orally administered KCN when expressed as cyanide (3.2 mg CN^-/kg bw) (Kruszyna et al., 1982). The dose-response for intraperitoneally administered KCN in mice indicated that 1 or 2 mg KCN/kg bw (0.4 or 0.8 mg CN^-/kg bw) had minimal or no effects, while 3-5 mg KCN/kg bw (1.2-2.0 mg CN^-/kg bw) resulted in signs of toxicity (convulsions, agitation) (Isom et al., 1982). A dose of 6 mg KCN/kg bw (2.4 mg CN^-/kg bw) resulted in 20% mortality. Doses that are fatal to one species may be harmless to others. An oral dose of 3.8 mg KCN/kg bw (1.5 mg CN^-/kg bw) was fatal to a dog in 155 minutes (Gettler and Baine, 1938) but a higher dose of 8 mg KCN/kg bw (3.2 mg CN^-/kg bw), equal to the LD_{50} in mice, had only minimal effects on guinea pigs (Basu, 1983). Rats tolerated much higher doses of cyanide (80 mg CN^-/kg bw/day) when mixed in the diet (Kreutler et al., 1978) than when administered by gavage at 4.0 mg CN^-/kg bw (Ferguson, 1962).

The LC_{50} in mice for inhaled HCN was 184 mg/m³ for 30 minutes (Matjak-Schaper and Alarie, 1982). Correlation of concentration and duration of exposure with effect was difficult due to the high variability in response even within the same species, in which some animals recovered from doses that were fatal to others (Haymaker et al., 1952). When the concentration of HCN was kept at 1000 mg/m³, the time it took for different species to die decreased in the order: monkey > goat > guinea pig = rat > rabbit = cat = mouse > dog (Barcroft, 1931). Therefore, monkeys were least sensitive; dogs were most sensitive.

Animals tolerated higher doses of cyanide when administered in the diet or in the drinking water during subchronic exposure (Hayes, 1967; Palmer and Olson, 1979). Rats receiving ~12 mg CN^-/kg bw/day in drinking water had significantly increased liver weights compared with controls, while rats receiving ~8 mg CN^-/kg bw/day in the diet did not (Palmer and Olson, 1979). No clinical signs of toxicity, effects on body weight, hematology and no histopathologic lesions were found in beagles that consumed 3 mg CN^-/kg bw/day (calculated from body weight data and amount of CN consumed) in the diet for 30 days (American Cyanamid Co., 1959). However, dogs receiving ≥0.27 mg CN^-/kg bw/day, administered in a capsule for 15 months, had degenerative changes in ganglion cells of CNS (Hertting et al., 1960). Subchronic exposure to cyanide by subcutaneous and intramuscular routes has resulted in histopathologic lesions in the brain and spinal cord of rats and monkeys (Lessell, 1971; Smith et al., 1963; Hurst, 1940) and changes in hematologic parameters in baboons (Crampton et al., 1979). Chronic dietary exposure to cyanides (~3.2 and 4.3 mg CN^-/kg bw/day) resulted in no effects clinically or histologically (Howard and Hanzal, 1955), but daily doses of ~30 mg CN^-/kg bw/day in the diet of rats resulted in changes in thyroid homeostasis, reduced body weight gain and moderate demyelination in the spinal cord (Philbrick et al., 1979).

Pertinent data regarding the carcinogenicity of cyanides were not located in the available literature. Cyanide may have antitumor activity (Perry, 1935; Brown et al., 1960). Negative results for KCN were obtained for mutagenicity in S. typhimurium strains TA1535, TA1537, TA1538, TA98 and TA100, with and without metabolic activation (De Flora, 1981); although in a recent study by Kushi (1983) mutagenic activity of HCN gas was found in S. typhimurium strain TA100. Cyanide was negative in a modified rec assay in B. subtilis (Karube et al., 1981). NaCN induced severe teratogenic effects in hamsters when administered by subcutaneously implanted osmotic minipumps that delivered cyanide at a rate of 3.3-3.4 mg CN^-/kg bw/hour (79.2-81.6 mg CN^-/kg bw/day) from days 6-9 of gestation (Doherty et al., 1982). There were no effects of dietary cyanide in a concentration of 500 mg CN^-/kg diet on the reproductive performance of pregnant rats fed KCN throughout gestation and lactation (Tewe and Maner, 1981a). Offspring that were continued on the test diet after weaning consumed less food and grew at a signficantly reduced rate compared to control offspring. The effects on the reproductive performance of pigs maintained on diets containing cyanide (30.3, 276.6 and 520.7 mg CN^-/kg diet) throughout gestation and lactation included reduced organ-to-body weight ratios of the thyroid in the medium-dose group relative to the low-dose group, of the spleen in the high-dose group relative to the medium- and low-dose groups and of the heart in the high-dose group relative to the low-dose group of fetuses (Tewe and Maner, 1981b). Treated sows had hyperplasia of kidney glomerular cells and accumulation of colloid and morphological changes in follicular cells of the thyroid.

VI. HEALTH EFFECTS IN HUMANS

Acute Exposure

The acute effects of cyanide exposure in humans have been well documented. Several reviews have described the effects of ingestion and inhalation of HCN, KCN and NaCN (Di Palma, 1971, Gosselin et al., 1976; NIOSH, 1976; Hartung, 1982). In addition, systemic toxicity on dermal exposure has been described.

Oral. Acute exposure to cyanide by the oral route has usually occurred from suicide attempts (NIOSH, 1976). Reports of fatal oral doses are in good agreement. These data are summarized in Table VI-1. Gettler and St. George (1934) estimated a lethal dose of cyanide, as hydrocyanic acid (HCN) to be 50 mg (0.71 mg/kg bw for a 70 kg human). Gettler and Baine (1938) reported that the minimum lethal orally absorbed dose of HCN was 0.5 mg/kg bw. A range of doses of 0.5-3.5 mg HCN/kg bw absorbed orally was quoted by Ermans et al. (1972). This range includes the 60-90 mg (0.86-1.29 mg/kg bw) range cited by Gosselin et al (1976). This range is equivalent to ~1 teaspoon of a 2% hydrocyanic acid solution. Ingestion of 50-100 mg (0.71-1.42 mg/kg bw) of NaCN or KCN can result in immediate collapse and respiratory arrest (Hartung, 1982). The minimum lethal dose of cyanide salts was quoted by Di Palma (1971) as 200 mg for adults (2.9 mg/kg bw), although suicide attempts usually involved ingestion of 1-6 g corresponding to "a spoonful." When this amount of cyanide is ingested, ~3.5 mg/kg bw has been absorbed before death results. Gastrointestinal absorption of inorganic cyanide salts is slower than pulmonary absorption of HCN, and the onset and severity of symptoms are delayed and diminished (see Absorption Section in Chapter III). The time-course of responses has been described by

TABLE VI-1

Fatal Oral Doses of Cyanide Compounds

Compound	Dose		Reference
	mg	mg CN^-/kg bw	
HCN	50	0.71	Gettler and St. George, 1934
HCN	--	0.5	Gettler and Baine, 1938
CN salts	200	2.9	DiPalma, 1971
HCN	--	0.5-3.5	Ermans et al., 1972
HCN	60-90	0.86-1.29	Gosselin et al., 1976
NaCN or KCN	50-100	0.71-1.42	Hartung, 1982

Di Palma (1971). Within 1-5 minutes after ingestion, chemoreceptor stimulation results in hyperventilation, the stomach lining becomes irritated and vomiting may occur. At 5-20 minutes, unconsciousness, convulsions, muscular contraction of the jaw, flushed and dry skin, rapid and irregular pulse and gasping occur. Vascular collapse, dilation of the pupils and cyanosis follow. Bodansky and Levy (1923) administered KCNS or KCN in a gelatin capsule on two consecutive days to 25 human subjects. On the first day, the subjects received 15 mg KCNS, and on the second day, 10 mg KCN. Assuming the average weight of a human to be ~70 kg, these amounts represent doses of 0.14 mg KCN/kg bw and 0.21 mg KCNS/kg bw (both equivalent to 0.06 mg CN^-/kg bw). All subjects effectively detoxified these doses, as determined by thiocyanate level measurements.

Liebowitz and Schwartz (1948) reported a case of a 60-year-old, 80 kg man who had attempted suicide by ingesting an estimated 3-5 g of KCN. At one-half hour after ingestion, he vomited. One-half hour later, on admission to the hospital, he was comatose, and gastric lavage was performed. At one-half hour after lavage, he regained consciousness, at 8 hours after admission he had short-lived lingering effects of nausea and weakness, and he subsequently fully recovered rapidly. The blood level of cyanide at 2 hours after admission was 0.2 mg HCN/mℓ. Assuming a blood volume of 6 ℓ, the investigators calculated that 1.2 g (15 mg/kg bw) of HCN was present in the circulating blood. This absorbed dose is at least 5 times the lethal dose of ingested KCN, and yet, the patient recovered. No apparent reason for his recovery was discovered; however, recovery from ingestion of cyanide salts is not unprecedented. Liebowitz and Schwartz (1948) cited 22 cases of recovery.

Inhalation. Of the different routes of exposure and the different compounds, inhalation of HCN gas results in the most rapid onset of poisoning, producing almost immediate collapse, respiratory arrest and death within minutes (Di Palma, 1971). NIOSH (1976) has compiled data from human case reports and animal studies to estimate concentration-response effects for humans (Table VI-2). This data indicates that airborne concentrations of HCN of 99-528 mg/m^3 are fatal in 30-60 minutes. However, some reports indicated no injury at concentrations as high as 550 mg/m^3 for 1 minute, while others report that 297 mg/m^3 is immediately fatal. The 1-minute LC_{50} for humans was given as 3744 mg/m^3. Discrepancies may be due to individual variations and, in some cases, the problems inherent in extrapolating data from animal experiments in order to predict human responses.

Barcroft (1931) placed a man (70 kg) and a dog (12 kg) in an inhalation chamber and exposed them simultaneously to HCN at concentrations of 550-688 mg/m^3. After 50 seconds, the dog became unsteady; at 1.25 minutes, the dog collapsed and was unconscious; at 1.5 minutes, the dog had tetanic convulsions. One second later (91 seconds of exposure), the man emerged from the chamber, put on a respirator, but felt no symptoms. Two seconds later, the dog was believed to be dead (it recovered, and was walking around the next morning). Within a few minutes after exposure, the man felt briefly nauseated and had difficulty concentrating.

According to Di Palma (1971), acute exposure of humans to inhalation of ~2200 mg HCN/m^3 results first, in shortness of breath, local irritation to the throat and a feeling of warmth. Following a period of rapid breathing and sometimes an outcry, apnea, gasping, collapse, convulsions and often

TABLE VI-2

Reported (Estimated) Human Responses to Various Concentrations of HCN Vapors[a]

Reponses	Concentration (mg/m^3)[b]
Estimated LC_{50} for 1 minute exposure	3778
Nausea and difficulty concentrating after 91 second exposure	550-688
No serious consequences in 1 minute	550
No injury in 1 minute	550
No injury in 1.5 minutes	413
Immediately fatal	297
Rapidly fatal	330
Fatal in 6-8 minutes	297
No injury in 2 minutes	275
Fatal after 30 minutes	243-528
Fatal after 10 minutes	199
Fatal after 30 minutes	149
Fatal after 30-60 minutes	121-149
Fatal after 30-60 minutes	110-264
Fatal after 60 minutes	99
Fatal or immediately dangerous to life	99
Numbness, vertigo, weakness, nausea, rapid pulse, flushed face and headache	>55

TABLE VI-2 (cont.)

Reponses	Concentration (mg/m^3)[b]
Tolerated for 30-60 minutes without immediate or after effects	50-59
Complaints of headache, nausea, vomiting, cardiac symptoms	50
Minimal symptoms after several hours of exposure	22-44
Effects after several hours of exposure	20-40
No symptoms after 6 hours	20-40
Some headache, vertigo	5.5-20
No observed effect	0-19; mean 5.4
Fatigue, headache, body weakness, tremor, pain, nausea	5.5-14.3
Headache, weakness, changes in taste and smell, throat irritation, nausea, effort dyspnea, enlarged thyroids, changes in blood chemistry	4.6-13.6; mean, 9.1
Increased thiocyanate excretion in urine, but to a lesser extent than in cigarette smokers; no other effects noted	2.2-8.8; mean 5.5
No effects	0.11-0.99
Slight decrease in leukocytic activity of cytochrome oxidase, peroxidase and succinate dehydrogenase after an average of 5.4 years of exposure	0.25

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[a] Source: NIOSH, 1976

[b] The concentrations in mg/m^3 were calculated from concentrations expressed in ppm by multiplying by 1.1.

cardiac arrest occur within minutes. It was estimated that rapid death results from an absorbed dose of as little as 0.7 mg HCN/kg bw. At lower airborne concentrations (~5-50 mg/m^3) (see Table VI-1), symptoms include dizziness, numbness, weakness, headache, nausea and vomiting, confusion, rapid breathing and rapid pulse (NIOSH, 1976; Hartung, 1982). Wexler et al. (1947) found that intravenous injection of 0.11-0.2 mg NaCN/kg bw (roughly equivalent to 0.06-0.11 mg HCN/kg bw absorbed following inhalation, as estimated by ratio of molecular weights) in humans resulted in sinus pause and irregularly slowed heart rate, followed by an increased pulse above control.

Cyanide has a characteristic odor of bitter almond; however, the ability to smell cyanide is controlled by a sex-linked recessive gene (Kirk and Stenhouse, 1953).

Dermal. Absorption of HCN or solutions of cyanide salts through the skin may result in effects similar to the sublethal effects of inhalation exposure (Potter, 1950). Local effects to the skin such as dermatitis and rash may also result (Drinker, 1932; NIOSH, 1976). An LD$_{50}$ for dermal absorption of HCN, which is much slower than pulmonary absorption, was estimated as 100 mg/kg bw (Di Palma, 1971).

Subchronic and Chronic Exposure

Oral. Pertinent data regarding chronic oral exposure of humans to hydrocyanic acid, KCN and HaCN were not located in the available literature. There is a body of literature on the etiology of thyroid disorders and neuropathies characterized by optic atrophy, nerve deafness and spinal ataxia in people living in certain tropical areas of Africa, where the staple diet consists largely of cassava (Monekosso and Wilson, 1966; Osuntokun, 1968, 1972; Osuntokun et al., 1969, 1970; Makene and Wilson, 1972; Ermans et al., 1972; Delange and Ermans, 1971). Cassava is a root food that contains a high level of the cyanogenic glycoside, linamarin. Linamarin releases cyanide on metabolism or acid hydrolysis *in vivo*; therefore, exposure is not to cyanide per se. Tropical neuropathies have also been associated with such factors as infections, protein deficiency, riboflavin deficiency, vitamin B_{12} (cobalamin) deficiency or defective B_{12} metabolism (Osuntokun, 1968; Osuntokun et al., 1969; Makene and Wilson, 1972). Ingestion of cassava, in combination with iodine deficiency, has been associated with high incidences of goiter and cretinism in Zaire (Delange and Ermans, 1971; Ermans et al., 1972). In these cases, thiocyanate, an antithyroid agent formed from cyanide metabolism may be the toxicant.

Inhalation.

Cigarette Smoke -- Inhalation exposure to cyanide in tobacco smoke by heavy smokers has been associated with the condition of tobacco amblyopia, characterized by a loss of visual acuity; Leber's hereditary optic atrophy, a similarly manifested disorder; and with retrobulbar neuritis complicating pernicious anemia and optic atrophy (Wokes, 1958; Pettigrew and Fell, 1972, 1973; Wilson and Matthews, 1966; Foulds et al., 1968; Wilson, 1983). These disorders appear to involve defective metabolism of cyanide to thiocyanate, as well as a deficiency in vitamin B_{12} or defective vitamin B_{12} metabolism. In a recent review, Wilson (198[illegible] discussed these interrelationships, and a discussion of the mechanism is presented in Chapter VII.

Smoking during pregnancy is associated with a higher risk of giving birth to low body weight infants and of perinatal death (Andrews, 1973). Andrews (1973) compared plasma thiocyanate levels in maternal and cord blood taken at delivery from 21 women who had smoked during pregnancy and from 22 women who had not. For both maternal and cord blood, smokers (>10 cigarettes/day) had significantly higher levels of thiocyanate than did nonsmokers ($p<0.001$). Although no differences were found for infant weight, duration of gestation or onset of labor, group sizes were small (21 smokers, 22 nonsmokers). This study demonstrates the potential for intra-uterine exposure.

Occupational Exposure.

Case Studies -- Chronic exposure to the cyanides by the inhalation and dermal routes involves occupational exposure of persons engaged in case hardening and polishing of metals and photographic materials workers. Sandberg (1967) described a case of a goldsmith apprentice. In the course of his work, the man cleaned goldware 5-10 times daily for 4 years. The cleaning solution was prepared by adding 15 g KCN to a liter of water, heating to boiling and adding 50 mℓ of hydrogen peroxide. This procedure caused spattering on the skin. His symptoms included headaches, listlessness, partial paralysis of his left arm and left leg, a grayish pallor and partial loss of vision in the left eye. Hardy et al. (1950) described a case-hardener who had been consistently exposed to HCN in his work. His symptoms included headaches, episodes of dizziness, confusion, muscular weakness, poor vision, slurred speech, abdominal cramps, tremor, body rash and an enlarged thyroid. In another case, a man who had been frequently exposed to cyanide for 5 months while working as a machinist developed a goiter. The thyroid enlargements in these two cases were presumed to be a result of the action of thiocyanate formed upon metabolism of cyanide. Many additional cases of chronic occupational exposure to cyanide of individuals who developed similar conditions have been reviewed by NIOSH (1976).

Epidemiologic Studies. NIOSH (1976) has reviewed several epidemiologic studies, the reports of which have been published in foreign languages. These studies (Saia et al., 1970; Carmelo, 1955; Dinca et al., 1972; and Radojicic, 1973), as well as two studies published in English, one conducted in Egypt (El Ghawabi et al., 1975) and one in India (Chandra et al., 1980), are summarized in Table VI-3. Typical symptoms and manifestations of cyanide poisoning were observed in each study, with the exception of the study by Dinca et al. (1972), who looked only at enzyme activity. NIOSH (1976) questioned the validity of the techniques in measuring enzyme activity. Blood smears were stained for detection of enzyme granules in neutrophilic leukocytes. In the study of Carmelo (1955), the original exposed cohort had consisted of 600 fumigators who had experienced acute episodes of intoxication. Their symptoms were typical. In the study of El Ghawabi et al. (1975), the study groups had been instructed to avoid foods containing cyanogenic and thiocyanogenic glucosides (e.g., cabbage-like vegetables) (Ermans et al., 1972). The increased mean uptake of ^{131}I by the exposed workers, who had not been at work for 2 days prior to the determination, was explained as a response to acute cyanide withdrawal. Chandra et al. (1980) also instructed the subjects to avoid cyanogenic foods. In addition, data from smokers and non-smokers were analyzed separately. Smokers showed higher levels of cyanide and thiocyanate in their blood and urine.

TABLE VI-3

Summary of Epidemiologic Studies of Cyanide Exposure[a]

Study Population	Control Population	Duration of Exposure	Level of Exposure	Effects	Reference
36 male electroplaters from 3 factories in Egypt Age: 30-50+ years All were non-smokers	20 normal male workers of same age and socio-econimic status, with no exposure to cyanide All were non-smokers	5-15 years	Mean concentration of HCN in breathing zone was 7.1, 8.9 and 11.4 mg/m^3 for the 3 factories	Of the 36 exposed men, the following incidences were recorded: headache-29, weakness-28, changes in smell and taste-28, giddiness-20, throat irritation-16, vomiting-16, difficulty breathing-16, lacrimation-9, precordial pain-7, excessive salivation-3, difficulty focusing eyes-3, psychosis (confusion, hallucination, slurred speech)-2. The incidence of these symptoms were much lower in controls. 20 of the exposed men had mild to moderate thyroid enlargement. The exposed workers had significantly higher uptake of ^{131}I by the thyroid 4 and 24 hours after administration than the controls ($p<0.001$). The exposed group had significantly higher hemoglobin and lymphocyte counts ($p<0.001$).	El Ghawabi et al., 1975
23 (of 40 male workers) were available for study from a factory engaged in electroplating and casehardening in India Age: 23-40 years	20 male workers of the same age and socio-economic status with no exposure to cyanide or other hazardous chemicals	NR The study was conducted during months of May and June	Airborne concentration in workroom was 0.2-0.8 mg/m^3, mean, 0.45 mg/m^3 Airborne concentration in breathing zone was 0.1-0.2 mg/m^3, mean, 0.15 mg/m^3	Exposed workers had significantly higher levels of cyanide and thiocyanate in blood and urine than the control group. The exposed workers complained of typical symptoms	Chandra et al., 1980
21 workers of a galvanizing department who worked near cyanide vats and 19 wire hardeners and zinc platers	22 men who washed the wire in caustic soda	NR	NR	The exposed group had twice the incidence of insomnia, disturbed sleep, tremors, dermatitis (thought to be due to poor work habits), nosebleed and vertigo. The control group had relatively high incidences of headache, dizziness, buzzing in ears, irritation of eyes, cold sweat, poor digestion, abdominal pain, muscle weakness and shortness of breath (they worked with caustic soda).	Saia et al., 1970

TABLE VI-3 (cont.)

Study Population	Control Population	Duration of Exposure	Level of Exposure	Effects	Reference
13 HCN fumigators who had suffered acute episodes of HCN poisoning with loss of consciousness	4 HCN fumigators who did not report acute episodes of of HCN poisoning	1-27 years	NR	The 13 intoxicated men had high incidences of nervous disorders, such as, disturbance of equilibrium, vertigo, rapid eye movement, moebius sign (inability to maintain conversion of eyes in exopththalmic goiter). Precordial pain was a complaint of 9 of the 13 men, 11 had EKG abnormalities, 11 had hypertropic gastritis. None of the 4 controls had stomach or intestinal disorders.	Carmelo, 1955
31 men, 12 women in Romania who worked in metal galvanizing with chronic exposure to airborne HCN Age: 18-49 years Mean - 36 years	no details of control group	0.25-16 years mean: 5.4 years	Average exposure for last 5 years: 0.26 mg/m^3	Significantly decreased activity of cytochrome oxidase compared with controls. Considerably reduced activity of peroxidase and succinodehydrogenase.	Dinca et al., 1972
43 electroplaters and annealers in Yugoslavia exposed to cyanide	20 non-exposed workers	NR	7-11 mg/m^3	Most of the exposed workers had symptoms of fatigue, headache, weakness, tremor of hands and feet, pain and nausea. Exposed workers had higher urinary thiocyanate levels than non-exposed workers.	Radojicic, 1973

*The studies of Saia et al., 1970; Carmelo, 1955; Dinca et al., 1972 and Radojicic, 1973 were cited in NIOSH, 1976.

NR = Not reported

High Risk Subpopulations

Pregnant women who smoke may increase the susceptibility of their infants to toxic effects of cyanide. Smoking during pregnancy has been linked to low-weight of infants and perinatal death, and higher plasma thiocyanate levels were found in cord blood of smokers than non-smokers (Andrews, 1973).

A metabolic disturbance in the conversion of cyanide to thiocyanate and vitamin B_{12} deficiency have been associated with such conditions as tobacco amblyopia, Leber's hereditary optic atrophy and retrobulbar neuritis in people who are exposed to excess cyanide in tobacco smoke (Wilson, 1983). Excess exposure to cyanide and iodine deficiencies has been associated with thyroid abnormalities, such as goiter and cretinism (Delange and Ermans, 1971; Ermans et al., 1972). Neuropathies have been associated with increased cyanide exposure due to chronic dietary intake of cassava as a staple food, in combination with protein deficiency, riboflavin and vitamin B_{12} deficiencies and infections (Osuntokun et al., 1969; Osuntokun, 1968; Makene and Wilson, 1972). Therefore, individuals with a metabolic defect in the rhodanese system (the enzyme that transfers sulfur to cyanide, see Metabolism Section in Chapter III), a vitamin B_{12} deficiency or defective B_{12} metabolism or iodine deficiency, and fetuses exposed *in utero*, are at a higher risk to the toxic effects of excessive cyanide intake than the general population.

Summary

Acute oral exposure to cyanide has usually occurred from suicide attempts. Fatal orally absorbed doses range from 0.5-3.5 mg HCN/kg bw

(Gettler and St. George, 1934; Gettler and Baine, 1938; Ermans et al., 1972; Gosselin et al., 1976). The minimum lethal dose of orally ingested cyanide salts is ~2.9 mg/kg bw (Di Palma, 1971). When 1-6 g ("a spoonful") is ingested, ~3.5 mg/kg bw has been absorbed by the time of death. Within 20 minutes of exposure to fatal doses, events progress from hyperventilation, vomiting, unconsciousness, convulsions, rapid and irregular heart rate, gasping, vascular collapse and cyanosis, to death. Several cases of recovery have been reported after ingestion of cyanide at doses which have proved fatal in other cases (Liebowitz and Schwartz, 1948).

Inhalation of HCN is the most rapid route of fatal exposure and poisoning. The 1-minute LC_{50} for humans was reported as 3744 mg/m^3 (NIOSH, 1976). Acute exposure of humans to ~2200 mg HCN/m^3 results in shortness of breath, irritation to the throat and warmth followed by rapid breathing, an outcry, apnea, gasping, collapse, convulsions and death in minutes (Di Palma, 1971). As little as 0.7 mg HCN/kg bw absorbed after inhalation may result in rapid death. Many people are unable to smell cyanide, which has the odor of bitter almond, due to a sex-linked recessive gene (Kirk and Stenhouse, 1953). Sublethal concentrations (5-50 mg/m^3) result in dizziness, confusion, headache, nausea, numbness and hyperventilation (NIOSH, 1976). Acute dermal exposure produces similar effects, although much more slowly (Potter, 1950; Di Palma, 1971).

Chronic oral exposure to HCN, KCN or NaCN has not been described. People living in tropical areas of Africa consume cassava as a staple food, which contains high levels of linamarin, a cyanogenic glycoside that releases cyanide on metabolism or acid hydrolysis _in vivo_ (Osuntokun et al., 1969; Osuntokun, 1968; Makene and Wilson, 1972). These people have high incidences of neuropathies, associated with cyanide, vitamin B_{12} deficiency, protein deficiency and infections. Ingestion of cassava, together with iodine deficiency, has been associated with the etiology of goiter and cretinism (Ermans et al., 1972, Delange and Ermans, 1971).

Chronic exposure to cyanide has been associated with tobacco amblyopia in heavy cigarette smokers, Leber's hereditary optic atrophy and retrobulbar neuritis (Wilson, 1983). A defect in cyanide metabolism and vitamin B_{12} deficiency appear to be involved in these disorders. Smoking during pregnancy may result in low birth-weight infants (Andrews, 1973).

Case studies and epidemiologic studies of metal case-hardeners and HCN fumigators, occupationally exposed to cyanide fumes, describe effects in workers typical of sublethal cyanide poisoning, including headache, dizziness and thyroid enlargement (NIOSH, 1976).

VII. MECHANISMS OF TOXICITY

Acute

The mechanism by which cyanide exerts its acute toxic effects is well understood and has been reviewed in numerous reports. The following discussion is based on reviews by Di Palma (1971), Gosselin (1976), U.S. EPA (1980), Solomonson (1981) and Hartung (1982).

The cyanide ion can be formed _in vivo_ by dissociation of HCN, KCN, NaCN and any other cyanogenic compounds. The ion has a high affinity for many biologically active metal ions. It forms a stable complex with iron in the ferric state (Fe^{+++}). Cytochrome oxidase, the terminal enzyme in the mitochondrial electron transport chain, forms a stable complex with HCN (Honecker and Staunard, 1948). The inactivated enzyme is unable to catalyze the reaction:

$$\text{Reduced cytochrome} + 0.5\ O_2 \xrightarrow{\text{cytochrome oxidase}} \text{cytochrome} + H_2O,$$

resulting in inhibition of cellular respiration. The inhibition results in a histotoxic hypoxia since cells are unable to utilize oxygen. Oxidative phosphorylation is unable to proceed, and there is a shift to anaerobic metabolism with resultant accumulation of lactate, pyruvate and glucose. The cells cannot use oxygen delivered by oxyhemoglobin, thus, venous blood appears bright red since hemoglobin continues to carry oxygen. The central nervous system (CNS) and the heart are particularly sensitive to hypoxia, and the expected gross toxic effects are manifested. The time course for these events is very rapid and death can ensue in minutes (DiPalma, 1971).

Cyanide is capable of complexing with many enzymes and compounds that contain Fe^{+++} including catalase, peroxidase and methemoglobin. Cyanide can also form complexes with compounds that contain metals other than iron such as hydroxycobalamin (vitamin B_{12a}), phosphatase, tyrosinase, ascorbic acid-oxidase, xanthine oxidase and succinic dehydrogenase (Di Palma, 1971). However, the reaction with cytochrome oxidase is the most important for the onset of the acute toxic effects.

As discussed in Chapter III, cyanide is detoxified by the action of the enzyme rhodanese (Lang, 1933), the trivial name for cyanide sulfurtransferase. The enzyme transfers sulfur from a sulfur donor to cyanide to form the less toxic thiocyanate which is excreted in the urine (Williams, 1959). The major site of rhodanese activity in most species (rat, rabbit, monkey) is the liver (Himwich and Saunders, 1948), with particular localization in mitochondria (de Duve et al., 1955). The rate-limiting factor in cyanide detoxication, therefore, is the availability of an intramitochondrial sulfur donor. Minor detoxification pathways have been discussed in the Metabolism Section in Chapter III.

Chronic

The effects of chronic cyanide exposure are neurological in nature (see Subchronic Exposure Section in Chapter V and Subchronic and Chronic Exposure Section in Chapter VI). Repeated insults to neurological tissue resulting in histotoxic hypoxia may be responsible for the demyelination and necrosis of many tissues of the CNS, including the optic nerve (Ferraro, 1933; Lessell, 1971; Lessell and Kuwabara, 1974; Smith et al., 1963). Wilson (1983) has reviewed the role of cyanide in human diseases. Tobacco amblyopia, associated with heavy smoking and vitamin B_{12} depletion, and retrobulbar neuritis may be the result of abnormal cyanide and vitamin B_{12} metabolism (Wilson, 1983; Wokes, 1958). These conditions are effectively treated with hydroxycobalamin (vitamin B_{12}) which can react with cyanide to form cyanocobalamin (Wilson et al., 1971). If there were a defect in cyanide conversion to thiocyanate, and vitamin B_{12} were unavailable to detoxify the accumulated cyanide, neurological disorders would occur. Similar interrelationships may be involved in the etiology of such disorders as Leber's hereditary optic atrophy (Wilson, 1983). Neuropathies and amblyopias among people living in the tropical areas, especially in Africa, where cassava, a root food rich in the cyanogenic glycosides, linamarin and lotaustralin, is a dietary staple, may also involve vitamin B_{12} deficiency. In these disorders, many complicating factors, such as protein and other vitamin deficiencies, may also be involved (Wilson, 1983). The interrelationships between cyanide, thiocyanate, vitamin B_{12} and inherent defects in the metabolic control of the conversions are not completely understood. One suggestion was that cyanide, formed _in vivo_ from thiocyanate by the enzymatic action of thiocyanate oxidase in red blood cells (Goldstein and Rieders, 1953) (see Distribution and Metabolism Sections in Chapter III), may reach levels that are chronically toxic if there is a deficiency in vitamin B_{12}. Therefore, vitamin B_{12} may play a role in the regulation of cyanide metabolism. Increased blood levels of thiocyanate resulting from ingestion of cyanogenic foods, in combination with iodine deficiency, may play a role in the etiology of goiter and cretinism among inhabitants of the tropics (Ermans et al., 1972; Delange and Ermans, 1971). Thiocyanate is known to inhibit the uptake of iodide by the thyroid, by competitively inhibiting the accumulation of iodide.

Synergism

Other chemicals known to inhibit cytochrome oxidase are sulfide and azide (Smith and Gosselin, 1979; Smith et al., 1977), and they may as such have a synergistic or additional effect on cyanide toxicity. Sulfide is a more potent inhibitor of cytochrome oxidase than is cyanide, and may act by the same mechanism (Nicholls, 1975; Smith et al., 1977). Basu (1983) found that guinea pigs pretreated with ascorbate prior to oral administration of KCN developed a 100% incidence of severe tremor, ataxia, muscle twitches, paralysis and convulsion compared with only slight tremors in 38% of the animals treated only with KCN. It was postulated that ascorbate ties up cysteine so that it cannot act as a sulfur donor for the enzymatic action of rhodanese to convert cyanide to thiocyanate (see Metabolism Section in Chapter III). Administration of cysteine had a protective effect on the enhanced toxicity of ascorbate plus cyanide.

Antagonism

Since cyanide acts by inhibiting cytochrome oxidase, thereby inhibiting the cellular utilization of oxygen, oxygen is not an antagonist of cyanide toxicity (U.S. EPA, 1980). Since cyanide can bind to Fe^{+++}, methemoglobin, which contains the ferric ion, can compete with cytochrome oxidase for cyanide, forming cyanomethemoglobin (Hartung, 1982; Way 1981). The use of sodium nitrite, hydroxylamine, amyl nitrite and other compounds capable of generating methemoglobin as antidotes to acute cyanide poisoning has its basis in this reaction (Smith and Olson, 1973; Way, 1981). Methylene blue has been used as an antidote in the past (Trautman, 1930), and its use may still be advocated by some physicians; however, it does not form methemoglobin as readily as the nitrites (Way, 1981).

Although oxygen in itself is not an antagonist, numerous studies have found that oxygen enhances the antidotal efficacy of the combination of sodium thiosulfate (a sulfur donor for the rhodanese reaction) and sodium nitrite (a methemoglobin generator) (Way et al., 1966a; Burrows et al., 1973; Isom and Way, 1974; Sheehy and Way, 1968). Schwartz et al. (1979) found that pretreatment of mice with pyruvate had a protective effect against cyanide poisoning. Pyruvate enhanced the antidotal effect of sodium thiosulfate, but not of sodium nitrite. When used in combination with sodium thiosulfate and sodium nitrite, maximum antidotal efficacy was observed.

Administration of compounds that can serve as sulfur donors for rhodanese may be a useful antidotal approach. Sorbo (1953) compared the effectiveness of many sulfur containing compounds and concluded that the structural requirements were for a free sulfur atom to be adjacent to another sulfur atom in the molecule. Frankenberg (1980) injected mice intravenously with bovine liver rhodanese and a sulfur donor following the administration of cyanide and found the enzyme to have an antidotal effect on cyanide poisoning.

Cobalt and cobalt containing compounds, such as vitamin B_{12} (hydroxocobalamin) (Mushett et al., 1952), cobalt-EDTA (Davison, 1969; Friedberg and Schwarzkopf, 1969) and cobaltous histidine (Friedberg and Schwarzkopf, 1969) have been used as effective antidotes to cyanide toxicity because of the affinity of cyanide for cobalt.

Summary

Cyanide exerts its acute toxic effect by forming a complex with Fe^{+++} in cytochrome oxidase, the terminal enzyme in the mitochondrial electron transport chain, thereby inhibiting utilization of oxygen by cells (Di Palma, 1971). The inhibition results in histotoxic hypoxia, preventing oxidative phosphorylation. There is a shift to anaerobic metabolism. The CNS and the heart are particularly sensitive to hypoxia, and toxicity is manifested. Cyanide can complex with other compounds that contain metals, but the reaction with cytochrome oxidase is the most important, toxicologically. Cyanide is detoxified by the enzymatic activity of rhodanese which transfers sulfur from a donor molecule to cyanide to form thiocyanate (see Metabolism Section in Chapter III).

Chronic cyanide exposure may contribute to the etiology of neurological and optical disorders (tobacco amblyopia, tropical neuropathy, Leber's hereditary optic atrophy), since repeated insults of hypoxia to neurological tissue results in demyelination and necrosis of many tissues of the CNS, including the optic nerve in animals (Ferraro, 1933; Lessell, 1971; Lessell and Kuwabara, 1974; Smith et al., 1963). Defects in cyanide metabolism, along with nutritional deficiencies of protein and vitamin B_{12}, are believed to be involved (Wilson, 1983). The goitrogenic effect of cyanide may be due to thiocyanate, which inhibits the uptake of iodine by the thyroid (Ermans et al., 1972).

Synergistic effects may occur if cyanide exposure is accompanied by exposures to other substances known to inhibit cytochrome oxidase, such as sulfide and azide (Smith and Gosselin, 1979). Ascorbate potentiated the toxicity of cyanide in guinea pigs, perhaps by reacting with cysteine and thereby preventing cysteine from acting as a sulfur donor for rhodanese (Basu, 1983).

Cyanide poisoning can be antagonized by methemoglobin, or any compound that can generate methemoglobin _in vivo_, such as sodium nitrite (Way, 1981). Oxygen enhances the antidotal efficacy of sodium thiosulfate and sodium nitrite (Way, 1981), as does pyruvate (Schwartz et al., 1979). Cyanide probably reacts with the carbonyl group of pyruvate to yield a cyanohydrin. Any compound that can act as a sulfur donor for rhodanese would be a cyanide antagonist (Sorbo, 1953), and treatment with rhodanese itself was an effective antidote (Frankenberg, 1980). Cobalt containing compounds have also been used as effective antidotes to cyanide poisoning (Mushett et al., 1952; Davison, 1969; Friedberg and Schwarzkopf, 1969).

VIII. QUANTIFICATION OF TOXICOLOGICAL EFFECTS

The quantification of toxicological effects of a chemical consists of an assessment of the noncarcinogenic and carcinogenic effects. In the quantification of noncarcinogenic effects, an acceptable daily intake (ADI) is calculated. An adjusted acceptable daily intake (AADI) and health advisory (HA) values for the chemical are then calculated to define the appropriate drinking water concentrations to limit human exposure. For ingestion data, this approach is illustrated as follows:

$$\text{ADI} = \frac{\text{(NOAEL or LOAEL in mg/kg/day) (body Weight in kg)}}{\text{Uncertainty/Safety Factor}} = \text{mg/day}$$

$$\text{AADI} = \frac{\text{ADI}}{\text{Drinking Water Volume in } \ell\text{/day}} = \text{mg/}\ell$$

where:

NOAEL = no-observed-adverse-effect level.

LOAEL = lowest-observed-adverse-effect level.

Body weight = 70 kg for adult or 10 kg for child.

Drinking water volume = 2 ℓ/day for adults or 1 ℓ/day for children.

Uncertainty/Safety Factor = 10, 100 or 1000.

Utilizing these equations, the following drinking water concentrations are developed for noncarcinogenic effects:

1. A 1-day HA for 10 kg child
2. A 1-day HA for 70 kg adult
3. A 10-day HA for 10 kg child
4. A 10-day HA for 70 kg adult
5. A lifetime AADI for a 70 kg adult

The distinctions made between the HA calculations (items 1 through 4) are associated with the duration of anticipated exposure. Items 1 and 2 assume a single acute exposure to the chemical. Items 3 and 4 assume a limited period of exposure (possibly 1-2 weeks). The HA values will not be used in establishing a drinking water standard for the chemical. Rather, they will be used as informal scientific guidance to municipalities and other organizations when emergency spills or contamination situations occur. The AADI value (item 5) is intended to provide the scientific basis for establishing a drinking water standard based upon noncarcinogenic effects.

A NOAEL or LOAEL is determined from animal toxicity data or human effects data. For animal data, this level is divided by an uncertainty factor because there is no universally acceptable quantitative method to extrapolate from animals to humans. The possibility must be considered that humans are more sensitive to the toxic effects of chemicals than are animals. For human data, an uncertainty factor is also used to account for the heterogeneity of the human population in which persons exhibit differing sensitivity to toxic chemicals. An Office of Drinking Water (ODW) modification of the guidelines set forth by the NAS (1977, 1980) is typically used in establishing uncertainty factors as follows:

- An uncertainty factor of 10 is used when good acute or chronic human exposure data are available and supported by acute or chronic toxicity data in other species.

- An uncertainty factor of 100 is used when good acute or chronic toxicity data identifying NOEL/NOAEL are available for one or more species, but human data are not available.

- An uncertainty factor of 1000 is used when limited or incomplete acute or chronic toxicity data are available or when only the acute or chronic toxicity data that identify a LOAEL (but not NOEL/NOAEL) for one or more species are available.

The uncertainty factor used for a specific risk assessment is judgmental. Factors that cannot be incorporated in the NAS/ODW guidelines for selection of an uncertainty factor, but must be considered include: 1) the quality of the toxicology data, 2) the significance of the adverse effect, and 3) the existence of counterbalancing beneficial effects.

If toxicological evidence requires the chemical to be classified as a potential carcinogen (however, there is insufficient evidence to classify cyanide as a carcinogen following oral exposure), mathematical models are used to calculate the estimated excess cancer risks associated with the ingestion of the chemical via drinking water. The bioassay data used in these estimates are from animal experiments. In order to predict the risk for humans, these data must be converted to an equivalent human dose. This conversion includes correction for noncontinuous animal feeding, nonlifetime studies and for the difference in size. The factor that compensates for the size difference is the cube root of the ratio of the animal and human body weights. It is assumed that the average human body weight is 70 kg and that the average human consumes 2 ℓ of water per day. The multistage model is then fit to the equivalent human data to estimate the risk at low doses. The upper 95% confidence limit of this estimate is used. Excess cancer risks can also be estimated using other models such as the one-hit model, the Weibull model, the logit model and the probit model. There is no basis in the current understanding of the biological mechanisms involved in cancer to choose among these models. The estimates of low doses for these models can differ by several orders of magnitude.

The scientific data base used to calculate and support the setting of risk rate levels has an inherent uncertainty. This is because the tools of scientific measurement, by their very nature, involve both systematic and random error. In most cases, only studies using experimental animals have been performed. There is thus uncertainty when the data are extrapolated to humans. When developing risk rate levels, several other areas of uncertainty exist: 1) incomplete knowledge concerning the health effects of contaminants in drinking water; 2) the impact of test animal age, sex and species and the nature of target organ systems examined on the toxicity study results; and 3) the actual rate of exposure of internal targets in test animals or humans. Dose-response data are usually only available for high levels of exposure, not for the lower levels of exposure for which a standard is being set. When there is exposure to more than one contaminant, additional uncertainty results from a lack of information about possible synergistic or antagonistic effects.

Noncarcinogenic Effects

Cyanides are readily absorbed from the lungs, the gastrointestinal tract and the skin by animals and humans. Inhalation exposure to hydrogen cyanide (HCN) provides the most rapid rate of entry, resulting in the most rapid onset of toxic effects. Absorption also occurs rapidly by ingestion of the cyanide salts, potassium cyanide (KCN) and sodium cyanide (NaCN) and, by dermal exposure to HCN, aqueous solutions of HCN (hydrocyanic acid), KCN and NaCN.

Several studies reported quantitative absorption data in animals and humans. Dogs that received single gavage doses of KCN equivalent to 20, 50 and 100 mg HCN (1.57, 4.42 or 8.40 mg HCN/kg bw, calculated using reported body weights of 12.7, 11.3 and 11.9 kg, respectively) absorbed 72% (14.4 mg or 1.13 mg/kg bw), 24% (12 mg or 1.06 mg/kg bw) and 16.6% (16.6 mg or 1.39 mg/kg bw), respectively, through the gastrointestinal tract (Gettler and Baine, 1938). These results suggest that the absolute amount absorbed was relatively constant and not related to the time between administration and death.

An 80 kg man was reported to have had a concentration of 0.2 mg/mℓ of cyanide in the blood 3 hours after ingestion of 3-5 g (37.5-62.5 mg/kg bw) of KCN. Assuming that the total blood volume wa 6 ℓ, then the vascular system contained an estimated total of 1200 mg. Assuming, further, that total body concentration was at least twice that in blood, then there were 2400 mg in the whole body (30 mg/kg bw). It should be noted that vomiting occurred 0.5 hours after ingestion and gastric lavage was performed immediately upon admission of the man to the hospital (Liebowitz and Schwartz, 1948).

Pettigrew and Fell (1973) found that in rats injected intraperitoneally with KCN at a dose equivalent to 0.6 mg CN^-/100 g bw, the cyanide levels in blood peaked at ~1.6 μg/g blood in 20 minutes, followed by a rapid decline. The plasma levels of thiocyanate rose to ~5 μg/g plasma at 1 hour and remained elevated for 4 hours, followed by a gradual decline. A detoxification rate of 0.076 mg/kg/minute was determined in guinea pigs during continuous intravenous infusion of cyanide (Lendle, 1964). The detoxification rate in humans has been estimated as 0.017 mg/kg/minute (McNamara, 1976). This estimate was based on a study in men injected intravenously with HCN.

The main site of cyanide detoxification is in the liver via the enzymatic action of rhodanese (the detoxifying enzyme in the liver) to form the less toxic thiocyanate. Differences among species with respect to distribution of rhodanese may account in part for differences among species with respect to sensitivity to cyanide. Dogs were found to have very low levels of rhodanese. Monkeys, rabbits and rats had hepatic levels ~10-18 times higher than dogs (Himwich and Saunders, 1948). Total levels of the enzyme in all tissues, except the adrenals, were lower in dogs than in the other species. Barcroft (1931) found that the dog was the most sensitive of eight species to inhalation exposure to cyanide. The maximum inhalation concentration of HCN (which ranged from 100-400 mg/m^3) that each species could survive was calculated. Dogs were the most sensitive, guinea pigs the least. When the concentration was held constant (at 1000 mg HCN/m^3), the time-to-death was calculated. Again, dogs were most sensitive, but in this case monkeys were least sensitive. Rats, mice, rabbits, cats and goats were of intermediate sensitivities in the two determinations. Levels of rhodanese in other species, including humans, have not been reported.

The major route of cyanide elimination from the body is via urinary excretion of thiocyanate. Rats eliminated 80% of subcutaneously-injected cyanide as thiocyanate in the urine, while 15% was eliminated as urinary 2-imino-4-thiazolidine carboxylic acid (Wood and Cooley, 1956). A man who had ingested 3-5 g (at least 1.2 g HCN was present in blood 3 hours later) eliminated a total of 237 mg thiocyanate in 72-hour urine (Liebowitz and Schwartz, 1948).

Okoh (1983) reported the pattern of elimination of ^{14}C in rats maintained on a diet of KCN (~2 mg CN^-/rat/day) for 6 weeks, and then injected subcutaneously with $Na^{14}CN$. Over 57% of the administered radioactivity was excreted in the 24-hour urine compared with 4.9% in expired air and 1.7% in feces. Thiocyanate accounted for 78.8% and cyanide for 1.3% of the urinary radioactivity. Of the radioactivity in expired air, 89.5% was $^{14}CO_2$ and 9.4% was $^{14}CN^-$. In a similar study, Okoh and Pitt (1982) also found radioactivity excreted in feces following intraperitoneal injection of $Na^{14}CN$. This finding, along with relatively high levels of radioactivity in the gastric mucosa and stomach contents compared with other tissues, suggested that gastrointestinal recirculation was occurring. Boxer and Rickards (1952a) observed low levels of unchanged HCN in expired air of rats and humans. Guinea pigs eliminated 1-2% of intravenously-infused NaCN as HCN gas in the expired air (Friedberg and Schwarzkopf, 1969).

Short-Term Exposure. In animals, acute LD_{50} values for cyanide range from ~0.91 mg CN^-/kg by intramuscular administration in rabbits, to 6.3 mg CN^-/kg by oral ingestion in mice. Acute LD_{50} values are summarized in Table VIII-1. For comparison purposes all doses are presented as the dose of the administered compound as well as the equivalent dose of cyanide ion (CN^-).

Acute LD_{50} Values for Cyanides

Route	Administered Compound	Species/Strain	Age/Weight (g)	Sex/No.	Vehicle	LD_{50} (mg/kg bw)	LD_{50} (mg CN^-/kg bw)	Comment	Reference
Oral	KCN	rat/Sherman	adult/NR	M/NR	NR	10	4.0		Hayes, 1967
Oral	KCN	rat/Sherman	adult/NR	M/50	water	10	4.0	The rats died within 1 hour. LD_1 was 5.9 mg KCN/kg bw (2.4 mg CN^-/kg bw).	Gaines, 1969
Oral	KCN	mouse/Swiss-Webster	NR/NR	NR/20/group	water	10.8	4.3	The compound was administered in a volume corresponding to 5% bw.	Ferguson, 1962
						15.8	6.3	The volume corresponded to 1% bw.	
Oral	KCN	mouse/Swiss-Webster	NR/18-20	M/10/group	NR	8.5	3.4	The LD_{50} is for mice dying up to 24 hours after dose. Signs of toxicity appeared in 30-90 seconds. After a short period of convulsions, mice were moribund; many at doses below LD_{50} appeared dead but recovered.	Sheehy and Way, 1968
Ocular	HCN	rabbit/NR	NR/NR	NR/NR	see comment	1.05	1.01	It was stated that the toxicity of NaCN was not different whether applied in solution, as a solid or mixed with an inert powder. Deaths occurred in 3-12 minutes.	Ballantyne, 1983
	KCN					7.87	3.15		
	NaCN					5.05	2.68		
i.p.	NaCN	mouse/CD-1	NR/25-30	M/NR	water	6.0	3.2	Pretreatment of mice with hydroxylamine, dimethylaminophenol or sodium nitrite increased the LD_{50} of NaCN.	Kruszyna et al., 1982
s.c.	KCN	mouse/Swiss-Webster	NR/18-22	M/10/group	saline	8.5	3.4	LD_{50} increased by pretreatment with sodium nitrite and sodium thiosulfate.	Way et al., 1966a

Route	Administered Crmpound	Species/Strain	Age/Weight (g)	Sex/No.	Vehicle	LD$_{50}$ (mg/kg bw)	LD$_{50}$ (mg CN$^-$/kg bw)	Comment	Reference
s.c.	KCN	mouse/Swiss-Webster	NR/18-23	M/10/ group	saline	12.0	4.8	LD$_{50}$ increased by pretreatment with cobaltous chloride alone or in combination with sodium nitrite and/or sodium thiosulfate.	Isom and Way, 1973
s.c.	KCN	mouse/Swiss-Webster	NR/18-23	M/10/ group	saline	11.8	4.7	LD$_{50}$ increased by pretreatment with sodium nitrite and sodium thiosulfate, enhanced by O_2.	Way et al., 1972
s.c.	KCN	mouse/NR	NR/18-32	F/10/ group	saline	6.02 2.86	2.41 1.14	At 23-25°C At 4°C	Streicher, 1951
s.c.	NaCN	dog/NR	NR/NR	NR/16	NR	5.36	2.84	LD$_{50}$ increased by immediate post-treatment administration of sodium thiosulfate, amyl nitrite, sodium nitrite and combinations of antidotes.	Chen and Rose, 1952
i.m.	HCN	rabbit/NR	adult/NR	M/10-15/ group	water	1.50	1.44	Increased rate of breathing, vociferation, uncoordinated movement of head, ataxia, tremors, respiratory and cardiac arrest.	Ballantyne et al., 1971, 1972
				F/10-15/ group		0.95	0.91		
i.m.	KCN	rabbit/NR	adult/NR	M/10-15/ group	water	3.06	1.22	Same as above, the rabbits lived longer following KCN rather than HCN administration.	Ballantyne et al., 1971, 1972
				F/10-15/ group		3.27	1.31		

NR = Not reported

i.p. = intraperitoneal; s.c. = subcutaneous; i.m. = intramuscular

A dermal LD_{50} for HCN in humans has been estimated to be 100 mg/kg (DiPalma, 1971). A 1-minute LC_{50} for humans for exposure to HCN vapors is estimated to be 3778 mg/m³ (NIOSH, 1976).

Most of the studies on the health effects of oral exposure to cyanides in animals have been conducted using KCN, although NaCN has also been administered in some studies. Few studies on acute oral toxicity of cyanides providing dose-response data were encountered. Oral (via gastric intubation) doses of KCN equivalent to 4.0 and 6.0 mg CN^-/kg were fatal to rats and mice, respectively (Ferguson, 1962). Increasing the volume of water in which the dose was administered had the effect of increasing the incidence of death in the animals. There were no available data to indicate an effect of vehicle volume at sublethal doses.

Of 8 guinea pigs administered a single oral dose of KCN equivalent to 3.2 mg CN^-/kg, 5 had no signs of toxicity; the other 3 had slight tremors from which they recovered within 15 minutes (Basu, 1983). It should be noted that this low effect level in guinea pigs is equal to the LD_{50} in mice.

Rats can tolerate higher doses of cyanide when administered in the diet than when administered orally by gavage. The gastrointestinal absorption following intermittent ingestion of low doses of cyanide over a day may allow for sufficient detoxication to occur (see Chapter V). Sherman rats survived 25 daily doses of 4 mg CN^-/kg bw when given as KCN mixed with the food (Hayes, 1967). This daily dose is equal to the acute oral LD_{50} in aqueous vehicle in the same strain of rats.

Male Sprague-Dawley rats (70 g, 7 rats/group) tolerated KCN at a level of 0.08 mg CN^-/mℓ when KCN was dissolved in the drinking water for 21 days (Palmer and Olson, 1979). This dose can be calculated as 12 mg CN^-/kg/day by assuming that a young growing rat consumes an amount of water equal to ~15% of its body weight each day. The ingestion of water by rats is intermittent, thus gastrointestinal absorption is intermittent, as in the case of dietary doses. There was no effect on body weight gain, but there was a significant increase in the average liver weight when compared with controls ($p<0.05$). When the KCN was mixed in the food at a concentration equivalent to 80 mg CN^-/kg feed, a daily dose of 8 mg CN^-/kg bw (calculated by assuming that a young growing rat, in a subchronic study, consumes an amount of food equal to ~10% of its body weight per day), did not result in increased liver weight. Potassium cyanide in the diet may have been more slowly absorbed than KCN in water due to physical interference with absorption or possible influence of chemical interactions of cyanide with components of the food. The Sprague-Dawley rats used in this study (Palmer and Olson, 1979) were not examined histologically, but African giant rats (Cricetomys gambianus, Waterhouse), maintained on diets containing 1000 mg CN^-/kg diet (daily dose of 36 mg CN^-/kg bw) for 84 days did not have histopathologic lesions in the thymus, kidney, liver and spleen (Tewe, 1982). Thus, a daily dose of 8 mg CN^-/kg bw administered orally in food (Palmer and Olson, 1979) is a NOAEL for increased liver weight in rats.

In a dietary study conducted by the American Cyanamid Co. (1959), three male and two female beagle dogs received NaCN mixed with food for 30-32 days. One male and one female dog served as controls. Each meal, which the dogs consumed completely, contained 24 mg CN^-. The average weight of the dogs was 7.6 kg; therefore, the daily dose was ~3 mg CN^-/kg bw. A single gavage dose at this level in dogs resulted in death in another study (Gettler and Baine, 1938). Dogs receiving 1.5, 4.3 and 8.1 mg CN^-/kg bw as single oral doses of KCN died in 155, 21 and 8 minutes, respectively. In the American Cyanamid study the dogs tolerated the dietary dose because absorption may have been slowed due to the presence of food in the stomach. There were no effects during the dietary study on body weight, hemoglobin content, hematocrit or differential white cell count. No treatment-related histopathologic lesions or organ-to-body weight ratio changes were observed during exhaustive histologic examinations.

Isom et al. (1982) studied the dose-response relationship of intraperitoneally administered KCN in male Swiss-Webster mice (4/group). The dose-dependent toxic signs included agitation, uncoordinated movement, gasping, irregular breathing, convulsion, respiratory arrest and death. At doses of KCN equivalent to 0.4 and 0.8 mg CN^-/kg bw, these signs were "barely detectable." At doses of 1.2, 1.6 and 2.0 mg CN^-/kg bw, the mice started gasping, and had irregular respiration and convulsions within 2-3 minutes of cyanide administration. At 2.4 mg CN^-/kg bw, the toxic signs were more severe and 20% of the mice died. At doses >2.4 mg CN^-/kg bw (not specified), all the mice died within 4 minutes. Assuming that "barely detectable" means that the mice were slightly agitated and breathed slightly more rapidly, 0.8 mg CN^-/kg bw may represent a LOAEL and 0.4 mg CN^-/kg bw probably represents a NOAEL for intraperitoneally administered cyanide in mice. Because cyanide is rapidly absorbed from the gastrointestinal tract and is rapidly detoxified on first passage through the liver, the effects of intraperitoneal administration may well be equivalent to the effects of oral administration. Data shown in Table VIII-1 indicate that the intraperitoneal LD_{50} and the oral LD_{50} in mice (3.2 and 3.4 mg CN^-/kg bw, respectively) are essentially equivalent. Therefore, "barely detectable" signs of toxicity of cyanide at 0.4 and 0.8 mg CN^-/kg bw may represent a NOAEL and LOAEL, respectively, for orally administered cyanide in mice.

The administration of NaCN by osmotic minipumps, implanted subcutaneously in pregnant hamsters on days 6-9 of gestation, resulted in severe teratogenic effects (Doherty et al., 1982). The pumps delivered NaCN at rates of ~0.1275 mmole NaCN/kg bw or a daily dose of 150 mg NaCN/kg bw (80 mg CN^-/kg bw). This study has little relevance to the risk assessment due to the high dose of cyanide and the method of administration, which was chosen in order to mimic the slow release of cyanide from nitriles during *in vivo* metabolism.

In an acute study, a man and a dog were exposed to HCN gas (between 500 and 625 ppm) simultaneously in an inhalation chamber (Barcroft, 1931). The man mimicked the movements of the dog, to approximate the same degree of activity, until the dog collapsed and went into convulsion. The man then exited the chamber with no symptoms except mild nausea and a sense of confusion. The dog was removed from the chamber and was believed to be dead, but subsequently recovered. Therefore, the dog does not appear to be an appropriate model for human toxicity to cyanide.

Information on the acute effects of ingestion of cyanides in humans has been obtained from case reports of suicide attempts. For HCN taken orally, absorbed doses of 0.5-3.5 mg HCN/kg bw (0.48-3.4 mg CN^-/kg bw) are fatal

(Gettler and St. George, 1934; Gosselin et al., 1976; Ermans et al., 1972). Lethal doses of NaCN or KCN were reported to range from 50-200 mg or 0.7-2.9 mg/kg bw for a 70 kg human (~0.3-1.5 mg CN^-/kg bw) (Hartung, 1982; DiPalma, 1971). However, a case was reported in which a man recovered following ingestion of 3-5 g of KCN (at least 15 mg CN^-/kg bw was absorbed) (Liebowitz and Schwartz, 1948).

Bodansky and Levy (1923) administered cyanide orally in a capsule to 25 human subjects on 2 consecutive days. The capsules contained 15 mg of KCNS on the first day and 10 mg KCN on the second day. Assuming that the average body weight of humans is 70 kg, the doses were 0.21 mg KCNS and 0.14 mg KCN/kg bw or 0.06 mg CN^-/kg bw. The subjects effectively detoxified these doses as determined from measurements of thiocyanate levels in saliva. The subjects did not complain of any symptoms. While a daily dose of 0.06 mg CN^-/kg bw thus exerted no acute oral effect in humans, it does not necessarily represent the maximum no-effect level.

Long-Term Exposure. In a 2-year dietary study, Carworth Farms rats (10 animals/sex/group) were administered diets fumigated with HCN (Howard and Hanzal, 1955). Diets contained 0, 100 or 300 mg HCN/kg. Results of the residue analyses (done to measure evaporation loss) indicated that in 2 days the dietary concentration of HCN fell, on an average, from 100 to 51.9 mg/kg diet for the low-dose level and from 300 to 80.1 mg/kg diet for the high-dose level. The average daily low and high concentrations were ~76 and 190 mg HCN/kg diet (73 and 183 mg CN^-/kg diet). From data on reported food consumption and body weight, the estimated daily doses were 3.2 and 4.3 mg CN^-/kg bw for the low-dose males and females, respectively, and 7.8 and 10.4 mg CN^-/kg bw for the high-dose males and females, respectively.

There were no treatment-related effects on growth rate, no gross signs of toxicity, nor any effects on organ-to-body weight ratios for liver, kidney, spleen, brain, heart, adrenals or gonads. There were no histopathologic lesions of the heart, lung, liver, spleen, stomach, intestines, kidney, adrenal, testes, uterus, ovary, cerebrum or cerebellum. The number of animals histologically examined was not specified, but it was stated as a "representative" number. Thus, the daily doses of 3.2 and 7.8 mg CN^-/kg bw (for males) and 4.3 and 10.4 mg CN^-/kg bw (for females) appear to be no-effect levels for 2-year cyanide feeding to rats.

Philbrick et al. (1979) fed KCN in the diet to a group of 10 male rats (strain not specified) for 11.5 months at a concentration of 1500 mg KCN/kg diet (600 mg CN^-/kg diet). Another group of 10 rats served as the control. Assuming that a rat in a long-term feeding study consumes a quantity of food equal to ~5% of its body weight, the dietary level corresponds to a daily dose of ~30 mg CN^-/kg bw. When compared with controls, the treated rats had a 40% reduction in mean body weight gain, 53% decrease in plasma thyroxine levels and 68% decrease in thyroxine secretion rates. There were no definitive histopathologic lesions to thyroid, sciatic, optic or other neural tissue. Mild degenerative changes in the myelin of the spinal cord were observed. Thus, a daily dose of 30 mg CN^-/kg bw was a LOAEL for dietary cyanide in rats.

Hertting et al. (1960) treated three dogs orally with NaCN in a gelatin capsule for up to 14.5 months. There was one control dog. Treatments were as follows: dog I received a daily dose of 0.27 mg CN^-/kg bw for 13.5 months; dog II received a daily dose of 0.53 mg CN^-/kg bw for 16 weeks and then a daily dose of 2.2 mg CN^-/kg bw for ~10.5 months longer; dog III received a daily dose of 1.1 mg CN^-/kg bw for 14.5 months. When daily doses >0.53 mg CN^-/kg bw were administered, there were signs of acute intoxication immediately after dosing; however, recovery occurred in <0.5 hours. In all treated dogs, histologic examination revealed degeneration of central nervous system ganglion cells and necrosis and inflammation of Purkinje cells of the cerebellum. Thus, a no-effect level in dogs cannot be identified. The finding of histologic damage to the central nervous system of dogs following subchronic oral dosing with low levels of cyanide may reflect the greater sensitivity of dogs to cyanide poisoning. Dogs have a decreased ability to detoxify cyanide since levels of rhodanese are very low in the dog, especially in the liver, when compared with rats, rabbits and monkeys (Himwich and Saunders, 1948).

No information was available on chronic oral exposure of humans to HCN, KCN or NaCN. Chronic ingestion of cyanogenic plants, such as cassava, a root food that forms the staple diet of people living in certain tropical areas of Africa, has been associated with the etiology of neuropathies and thyroid disorders (Osuntokun, 1972; Delange and Ermans, 1971). Exposure, however, was to linamarin and lotaustralin, cyanogenic glycosides contained in cassava, in addition to cyanide per se. Other complicating factors, such as vitamin B_{12}, protein and iodine deficiencies also played a role (Wilson, 1983).

Quantification of Noncarcinogenic Effects

One-Day Health Advisory. No suitable study was identified from which to calculate 1-day health advisories (1-day HAs). The results of Bodansky and Levy (1923) refer to one arbitrarily chosen low dose of cyanide and provide little indication of permissible loads. Indeed, if these results were used, the resultant 1-day HAs would actually fall below those criteria estimated from the more extensive results for more prolonged exposure. Thus, it is recommended that the 1-day HA be set at the same level as the 10-day HAs.

Ten-Day Health Advisory. The study by Palmer and Olsen (1979) could be used for the derivation of the 10-day HAs because no quantitative data for human exposure were available. Using this data, the 10-day HA for a 10 kg child would be calculated as follows:

$$\text{10-day HA}_C = \frac{(8\ \text{mg CN}^-/\text{kg bw/day})\ (10\ \text{kg})}{(1\ \ell/\text{day})\ (500)}$$

$$= 0.16\ \text{mg CN}^-/\ell$$

where:

8 mg CN^-/kg bw/day = NOAEL for effects on liver weight or body weight in rats following a 21-day exposure via food (Palmer and Olson, 1979)

10 kg = assumed weight of a child

1 ℓ/day = assumed drinking water consumption by a 10 kg child

500 = uncertainty factor. An uncertainty factor of 100 is selected based upon the NAS/ODW guidelines in which a NOAEL from an animal study is used. An additional 5-fold uncertainty factor is selected because of the possible problems associated with the use of a dietary study to estimate a drinking water criterion.

The 10-day HA for a 70 kg adult is calculated as follows:

$$\text{10-day HA}_A = \frac{(8\ \text{mg CN}^-/\text{kg bw/day})\ (70\ \text{kg})}{(2\ \ell/\text{day})\ (500)}$$

$$= 0.56\ \text{mg CN}^-/\ell$$

where:

8 mg CN^-/kg bw/day = NOAEL for effects on liver weight or body weight in rats following a 21-day exposure via food (Palmer and Olson, 1979)

70 kg = assumed weight of an adult

2 ℓ/day = assumed drinking water consumption by a 70 kg adult

500 = uncertainty factor. An uncertainty factor of 100 is selected based upon the NAS/ODW guidelines in which a NOAEL from an animal study is used. An additional 5-fold uncertainty factor is selected because of the possible problems associated with the use of a dietary study to estimate a drinking water criterion.

However, it is recommended that the Lifetime HA of 0.75 mg/ℓ be used for the adult 1-day and 10-day HAs. The NOAEL of 10.8 mg/kg/day used for the Lifetime AADI comes from a study where the animals were exposed for 2 years; the 8 mg/kg/day NOAEL is from a study where animals were exposed for only 21 days. Therefore, because there were no adverse effects when the exposure was for a longer time at higher levels, the Lifetime AADI of 0.75 mg/ℓ would be protective for the adult 1-day and 10-day exposures also. The corresponding 1-day and 10-day HAs for a 10 kg child consuming 1 ℓ of water would be 0.22 mg/ℓ.

Adjusted Acceptable Daily Intake. The study by Howard and Hanzal (1955) has been selected to serve as the basis for a lifetime ADI and AADI because it is the only long-term study encountered for which a NOAEL was identified.

In deriving daily doses, certain assumptions and decisions are made as follows:

1. The HCN concentrations reported by the authors are converted to CN^- concentrations on a molecular weight basis.
2. The body weight data presented by the authors are used rather than employing the assumption that a rat weighs an average of 350 g over its lifespan (45 FR 79352, November 28, 1980). The average body weights for all exposure groups are estimated from the growth charts using linear interpolation to estimate missing data points.
3. The food consumption data presented by the authors are used rather than assuming an average food consumption for all dose groups.
4. Average CN^- concentrations over the life of the experiment are estimated from the data presented by the authors and by assuming that the rate of loss of HCN can be described by a first-order process.
5. It is inappropriate to use a net absorption coefficient to account for presumed differences in the absorption of CN^- in food vs. drinking water. However, there is a given measure of uncertainty associated with the use of a dietary study to estimate a drinking water criterion, thus, an additional 5-fold uncertainty factor is used.

Thus, the data are:

Dose Group	Average Concentration (mg CN^-/kg diet)	Average Food Consumption (av. g/rat/day)	Body Weight (g)
Low male	73	19.46	390
High male	160	18.50	394
Low female	73	14.69	232
High female	160	17.24	255

Average daily doses are calculated as follows:

low dose male:
$(73\ \text{mg}\ CN^-/\text{kg diet} \times 0.01946\ \text{kg})/0.390\ \text{kg} = 3.6\ \text{mg}\ CN^-/\text{kg bw/day}$

high dose male:
$(160\ \text{mg}\ CN^-/\text{kg diet} \times 0.01850\ \text{kg})/0.394\ \text{kg} = 7.5\ \text{mg}\ CN^-/\text{kg bw/day}$

low dose female:
$(73\ \text{mg}\ CN^-/\text{kg diet} \times 0.01469\ \text{kg})/0.232\ \text{kg} = 4.6\ \text{mg}\ CN^-/\text{kg bw/day}$

high dose female:
$(160\ \text{mg}\ CN^-/\text{kg diet} \times 0.01724\ \text{kg})/0.255\ \text{kg} = 10.8\ \text{mg}\ CN^-/\text{kg bw/day}$

The ADI for a 70 kg adult is calculated as follows:

$$\text{ADI} = \frac{(10.8\ \text{mg}\ CN^-/\text{kg bw})\ (70\ \text{kg})}{10 \times 10 \times 5}$$

$$= 1.5\ \text{mg}\ CN^-/\text{day}$$

where: 10.8 mg CN^-/kg bw = highest NOAEL for the following parameters: growth rate, general toxicity, organ-to-body weight ratios for liver, kidney, spleen, brain, heart, adrenals and gonads; histopathologic lesions to the heart, lung, liver, spleen, stomach, intestines, kidney, adrenal, thyroid, testes, uterus, ovary, cerebellum and cerebrum following a 2-year dietary study in rats (Howard and Hanzal, 1955). This NOAEL is derived by converting HCN concentrations to CN^- concentrations on a molecular weight basis, by data on food consumption provided by the investigators and by estimating the average body weights/dose group over the length of the experiment from the growth charts provided in the report.

70 kg = assumed weight of an adult

500 = uncertainty factor. An uncertainty factor of 100 is selected based upon the NAS/ODW guidelines in which a NOAEL from an animal study is used. An additional uncertainty factor of 5 is selected due to possible problems associated with the use of a dietary study to estimate a drinking water criterion.

The AADI is calculated as follows:

$$\text{AADI} = \frac{1.5\ \text{mg}\ CN^-/\text{day}}{2\ \ell/\text{day}}$$

$$= 0.75\ \text{mg}\ CN^-/\ell$$

where: 2 ℓ/day = assumed drinking water consumption by a 70 kg adult

This AADI calculation assumes 100% of the human exposure derives from drinking water. The AADI may be modified upon the availability of relative source contribution data providing human exposure estimates from food, air and possibly the occupational environment. The ultimate goal is to establish an AADI so that human exposure from all sources does not exceed the ADI.

Note that there is virtually no difference between the 10-day HA_A and AADI. The derivations of the numbers were done independently. The results indicate that there is little difference in short-term and chronic toxicity of cyanide. This is not unexpected due to the known mechanism of CN^- toxicity and its lack of bioaccumulation.

Carcinogenic Effects

Potassium cyanide was negative for reverse mutation in five strains of *Salmonella typhimurium*, with and without metabolic activation (DeFlora, 1981). A marginally positive response was obtained in strain TA100 with HCN gas (Kushi, 1983). Cyanide was also negative in a modified rec assay in *Bacillus subtilis* (Karube et al., 1981).

Quantification of Carcinogenic Effects

The lack of information concerning the carcinogenicity of cyanide precludes the calculation of doses associated with increased lifetime risks of 10^{-4}, 10^{-5} and 10^{-6}. The International Agency for Research on Cancer (IARC) has not evaluated the carcinogenic potential of cyanide (WHO, 1982).

Existing Guidelines and Standards

In the June 9, 1981, Errata for the Ambient Water Quality Criteria for Cyanides (U.S. EPA, 1980), an ADI of 7.6 mg/day was recommended, based upon an oral NOAEL in rats for chronic exposure of 10.8 mg/kg/day (Howard and Hanzal, 1955) and a 100-fold uncertainty factor. The ambient water quality criterion based on this ADI was 3.77 mg CN^-/ℓ and assumed that a 70 kg human consumes 2 ℓ of water and 6.5 g of fish per day with a bioconcentration factor of 1.0.

The U.S. PHS (1962) recommended that concentrations of cyanide in water supplies not exceed 0.2 mg CN^-/ℓ in order to protect human health. The value appears to be calculated from the TLV, which gives a water level of ~19 mg/ℓ followed by the application of a 100-fold uncertainty factor. This uncertainty factor was used due to the steep dose-effect relationship observed for cyanide when body levels exceed detoxification capacity. The U.S. PHS (1962) also recommended that concentrations in drinking water be kept below 0.01 mg CN^-/ℓ since this level or lower can be achieved by proper treatment.

A TLV for alkali cyanides in workroom air of 5 mg CN^-/m^3 is recommended by the ACGIH (1980) based upon irritation to the respiratory system as well as protection from the effects of chronic exposure. The TLV of 5 mg CN^-/m^3 was also recommended by NIOSH (1976) and adopted by OSHA (1981).

Special Considerations

The only special considerations identified for cyanide exposure were the potential effects to high risk subpopulations. Infants and fetuses may be at higher risk to cyanide. Cyanide exposure at high doses to pregnant hamsters resulted in severe teratogenic effects (Doherty et al., 1982). Andrews (1973) found that pregnant women who smoke have higher levels of plasma thiocyanate in blood than nonsmokers. It has been suggested that cyanide exposure may result in low body weight infants.

A metabolic disturbance in the conversion of cyanide to thiocyanate and vitamin B_{12} deficiency has been associated with such conditions as tobacco amblyopia and Leber's hereditary optic atrophy in persons who are exposed to excess cyanide in tobacco smoke (Wilson, 1983). Iodine deficiency, along with excess exposure to cyanide, may be involved in the etiology of such thyroid disorders as goiter and cretinism (Delange and Ermans, 1971; Ermans et al., 1972). Protein deficiencies, vitamin B_{12} and riboflavin deficiencies may subject people in the tropics who eat cassava, a cyanogenic plant, to increased risks of tropical neuropathics (Osuntokun, 1972; Osuntokun et al., 1969; Makene and Wilson, 1972). Therefore, individuals with a metabolic defect in the rhodanese system, a vitamin B_{12} deficiency or defective B_{12} metabolism, iodine deficiency, protein deficiency or fetuses exposed _in utero_, are at a higher risk to the toxic effects of cyanide exposure than the general population.

Additional groups at a higher risk may be strict vegetarians who may become vitamin B_{12} deficient and people unable to smell cyanide.

Summary

The recommended values for the 1-day and 10-day HAs for both adults and children and the lifetime AADI are summarized in Table VIII-2.

TABLE VIII-2

Summary of Quantification of Toxicological Effects

	Drinking Water Concentration (mg CN^-/ℓ)		Reference[a]
	10 kg Child	70 kg Adult	
1-day Health Advisory	b/	b/	--
10-day Health Advisory	0.22[c]	0.75	Palmer and Olsen, 1979
Lifetime AADI	d/	0.75	Howard and Hanzal, 1955

[a] Reference for NOAEL used in calculating HA or AADI values

[b] No suitable study identified; it is recommended that the 1-day HAs be set at the same levels as the 10-day HAs.

[c] Calculated from the NOAEL used for the Lifetime AADI.

[d] Not calculated because the child will not remain in the high risk population for a lifetime.

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